NOVEL BENZIMIDAZOLE COMPOUNDS

FIELD OF INVENTION

The present invention is directed to novel benzimidazole derivatives that possess antibacterial activity. The invention also is directed to compositions including the benzimidazole derivatives, and methods for using the same.

BACKGROUND OF THE INVENTION

Almost all the major classes of antibiotics have encountered resistances in clinical applications. The emergence of bacterial resistance to β-lactam antibiotics, macrolides, quinolones, and vancomycin is becoming a major worldwide health problem. The spread of antibiotic resistance among pathogenic bacteria imposes another serious problem for the clinical management of infectious diseases. Particularly, antibiotic resistance among Gram-positive bacteria (staphylococci, enterococci, and streptococci) is becoming increasingly serious. Entercococci, which are generally resistant to most antibiotics including penicillin, cephalosporin and aminoglycosides, used to be treated with either a combination of two antibiotics or vancomycin. However, with the recent increased use of vancomycin in methicillin-resistance Staphylococcus aureus (MRSA) infections and colitis due to colstridium fifficile, multiple resistant entercocccus faecium has been spreading. As such, the last resort for anti-infective diseases, the Vancomycin family of antibiotics, has now been gravely challenged in recent years due to the

emergence of MRSA strains in clinical practice. There is an urgent need to discover novel antibacterial agents other than analogues of existing antibiotics.

A considerable amount of attention has focused recently on new RNA-binding molecules for drug discovery. The interactions between RNA and biological macromolecules are clearly essential fore many vital processes in molecular biology. In addition, the excitement over RNA-based viruses has fueled an interest in the development of potential RNA inhibitors. RNA offers several selective advantages over DNA as a therapeutic agent. First, chromosomal DNA is packaged extensively, significantly limiting its accessibility to small molecule regents. Second, DNA repair systems are available in the cell, whereas analogous enzymes for RNA repair are virtually unknown. Finally, RNA exhibits a high level of diversity in terms of tertiary folding, and therefore will likely have a greater potential for selective targeting based on structure rather than sequence.

Historically, however, RNA-based drug discovery has proved to be extremely difficult, and only a few classes of compounds are known to bind RNA with SAR information, for example aminoglycosides and cationic peptides. Discovery of RNA binders using traditional high throughput assays such as fluorescence, filter binding, SPA, SPR, etc. has proved to be equally unsuccessful.

Recently, a MS-based high throughput-screening assay has been developed. See, Hofstadler, S. A.; Griffey, R. H. *Curr. Opin. Drug Discovery Dev.* **2000**, *3*, 423-431; Hofstadler, S. A.; Griffey, R. H. *Chem. Rev. (Washington, D. C.)* **2001**, *101*, 377-390; Griffey, R. H.; Greig, M. J.; An, H.; Sasmor, H.; Manalili, S. *J. Am. Chem. Soc.* **1999**, *121*, 474-475; Sannes-Lowery, K. A.; Griffey, R. H.; Hofstadler, S. A. *Anal. Biochem.* **2000**, *280*, 264-271; Griffey, R. H.; Sannes-Lowery, K. A.; Drader, J. J.; Mohan, V.; Swayze, E. E.; Hofstadler, S. A. *J. Am. Chem. Soc.* **2000**, *122*, 9933-9938, and Griffey, R. H.; Hofstadler, S. A.; Sannes-Lowery, K. A.; Ecker, D. J.; Crooke, S. T. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 10129-10133, each of which is incorporated herein by reference in its entirety.

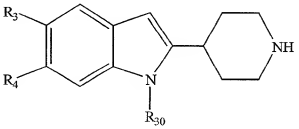
This assay is extremely sensitive and could detect RNA binders with Kd values ranging from nanomolar to minimolar. Coupled with mass assays to carry out competition experiments and determine the binding locations, such assays can be used to discover of novel compounds that bind to bacterial ribosomal RNA.

In view of the great importance of antibacterial compounds in animal, and particularly human health, it can be seen that there is a need for novel antibacterial agents. The present invention is therefore directed to, *inter alia*, such compounds and their uses, as well as other important ends.

SUMMARY OF THE INVENTION

The present invention also provides compositions containing the subject compounds, and methods for using the subject compounds. Methodologies for making the compounds of the invention are also disclosed. Other useful methodologies will be apparent to those skilled in the art, once armed with the present disclosure. These and other features of the compounds of the subject invention are set forth in more detail below.

In some embodiments, compounds are provided having the formula:

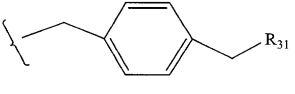


wherein:

R_3 and R_4 are independently each H, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, trihaloalkyl, alkoxycarbonyl, alkoxy, $NR_{15}R_{16}$, or NO_2;

R_{30} is C_{1-6} alkyl, heteroarylalkyl, arylalkyl, or heteroaryl, wherein each of said heteroarylalkyl, arylalkyl, or heteroaryl groups each can be optionally substituted with up to three substitutents selected from haloegn, NO_2, and mono-, di-, or trihaloalkyl;

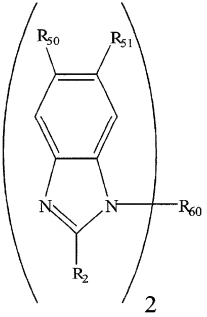
or R_{30} has the structure XX:



XX

wherein R_{31} is alkylamino, aminoalkylamino, poly(alkylamino)amino, heterocycloalkylamino, heterocycloalkyl, -NH-$(CHOH)_4$-CH_2OH, -NH-$(CH_2)_{1-12}$-heteroaryl or -NH-$(CH_2)_{1-12}$-heterocycloalkyl.

In a further aspect, the present invention provides dimeric benzimidazole compounds having the structure:



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wherein:

R_2 is NH_2 or piperidin-4-yl;

R_{50} and R_{51} are each independently selected from H, halogen, C_1-C_6 alkyl, trihaloalkyl, alkoxycarbonyl, alkoxy, $NR_{15}R_{16}$, and NO_2, wherein said C_1-C_6 alkyl, alkoxycarbonyl, and alkoxy groups can each be optionally substituted with $NR_{15}R_{16}$;

R_{15} is H, halogen, C_{1-12} alkyl, methylcarbonyl, heterocycloalkyl, arylsulfonyl, heteroarylalkyl, aminoalkyl, arylcarbonyl, branched and straight chain polyaminoalkyl, or a group of formula $CH_2(CHOH)_4CH_2OH$,

wherein said methylcarbonyl, heterocycloalkyl, arylsulfonyl, heteroarylalkyl, aminoalkyl, arylcarbonyl, and branched and straight chain polyaminoalkyl groups can be substituted by up to 3 OH groups;

R_{16} is H, halogen, or C_1-C_6 alkyl;

or R_{15} and R_{16} together with the nitrogen atom to which they are attached can form a succinimicdo or phthalimido group or a fused ring derivative thereof, wherein said succinimido or phthalimido group or fused ring derivative thereof can be optionally substituted by up to three substituents independently selected from NO_2 and halogen;

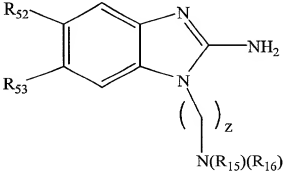
R_{60} is alkylene having from 1 to 18 carbons, or $-R_9$-X-R_{10}-)H;

R_9 and R_{10} are each independently alkylene having from 1 to about 20 carbons;

X is $-N(R_{12})$-, $-C(R_{13})(R_{14})$- or O; and

R_{12}, R_{13} and R_{14} are each independently H or C_1-C_6 alkyl.

In a further aspect, the present invention provides compounds of formula:



wherein:

R_{52} and R_{53} are each independently selected from H, halogen, C_1-C_6 alkyl, trihaloalkyl, alkoxycarbonyl, alkoxy, $NR_{15}R_{16}$, and NO_2, wherein said C_1-C_6 alkyl, alkoxycarbonyl, and alkoxy groups can each be optionally substituted with $NR_{15}R_{16}$;

R_{15} is H, halogen, C_1-$_{12}$ alkyl, methylcarbonyl, heterocycloalkyl, arylsulfonyl, heteroarylalkyl, aminoalkyl, arylcarbonyl, branched and straight chain polyaminoalkyl, or a group of formula $CH_2(CHOH)_4CH_2OH$;

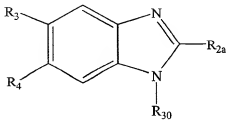
wherein said methylcarbonyl, heterocycloalkyl, arylsulfonyl, heteroarylalkyl, aminoalkyl, arylcarbonyl, and branched and straight chain polyaminoalkyl groups can be substituted by up to 3 OH groups;

R_{16} is H, halogen, or C_1-C_6 alkyl;

or R_{15} and R_{16} together with the nitrogen atom to which they are attached can form a succinimicdo or phthalimido group or a fused ring derivative thereof, wherein said succinimido or phthalimido group or fused ring derivative thereof can be optionally

substituted by up to three substituents independently selected from NO_2 and halogen; and z is 1 to 6.

Also privided by the present invention are compounds having the Formula:



wherein:

R_{2a} is amino, phenyl, mono- or bicyclic heterocycloalkyl having 1 or 2 ring nitrogen atoms, mono- or bicyclic heteroaryl having 1 or 2 ring nitrogen atoms, cycloalkyl, halogen, heterocycloalkylalkyl (i.e., alkyl sub w' heterocycloalkyl) having 1 or 2 ring nitrogen atoms, mono- or bicyclic heterocycloalkylamino having 1 or 2 ring nitrogen atoms or a group of formula -S-alkylene-L_1 where L_1 is mono- or bicyclic-heteroaryl having 1 or 2 ring nitrogen atoms;

wherein each of said amino, phenyl, heterocycloalkyl, heteroaryl, cycloalkyl, heterocycloalkylalkyl, or heterocycloalkylamino groups can be optionally substituted with a group selected from amino, OH, C_1-C_{12} alkyl, a structure of formula -C(=O)CH(NH_2)-L_2 where L_2 is the side chain of a naturally occurring alpha amino acid, $-C(NH_2)=NH$, C_1-C_{12} alkylcarbonyl, mono- or bicyclic heteroaryl having 1 or 2 ring nitrogen atoms, mono- or bicyclic heteroarylalkyl having 1 or 2 ring nitrogen atoms, or S-alkyl-heteroaryl where said heteroaryl is mono- or bicyclic having 1 or 2 ring nitrogen atoms; and

R_3 and R_4 are each independently halogen, amino, NO_2, CN, C_{1-6} alkoxy or C_{1-6} alkyl optionally substituted with up to 3 halogen atoms; and

R_{30} is H, alkyl, aryl, arylalkyl, heteroaryl; heteroarylalkyl, heterocycloalkyl, arylsulfonyl, aryloxycarbonyl, alkoxyalkoxyalkyl, alkyl-S-R_7, alkyl-NH-C(=O)-R_8 or $-R_9$-X-R_{10}-R_{11})H;

wherein each of the alkyl, aryl, arylalkyl heteroaryl, heteroarylalkyl, heterocycloalkyl, arylsulfonyl, aryloxycarbonyl and alkoxyalkoxyalkyl moieties in each of the foregoing R_1 groups can be optionally substituted with up to 3 groups independently selected from the group consisting of C_1-C_6 alkyl, OH, hydroxyalkyl, -C(=O)-R_5, CN, aryl, alkoxycarbonyl, alkylaryl, arylalkyl, heteroaryl, S-heteroaryl optionally substituted with halogen, heteroarylalkyl optionally substituted with halogen, heterocycloalkyl optionaly substituted with amino, NO_2, halogen, monohaloalkyl, dihaloalkyl, trihaloalkyl, perhaloaryl, perhaloalkylaryl, alkyl-$NR_{15}R_{16}$ and $NR_{15}R_{16}$;

or one of said alkyl, aryl, arylalkyl heteroaryl, heteroarylalkyl, heterocycloalkyl, arylsulfonyl, aryloxycarbonyl or alkoxyalkoxyalkyl moieties of one of said R_1 groups can be attached to a structure of Formula I at position R_1 thereof;

R_5 is H, –NHNHR_6, –NHN=CH-R_6, heteroaryl, heterocycloalkyl, wherein said hereteroaryl group can be optionally substituted with an aryl or heteroaryl group,

R_6 is aryl, heteroaryl; arylsulfonyl, heteroarylsulfonyl, -C(=S)-NH-aryl, -C(=S)-NH-arylcarbonyl, -C(=S)-NH-heteroarylcarbonyl, -C(=S)-NH-alkylene-R_{21}, -C(=O)-NH-aryl, -C(=O)-NH-arylcarbonyl, -C(=O)-NH-heteroarylcarbonyl, or -C(=O)-NH-alkylene-R_{21} where R_{21} is carboxy, alkoxycarbonyl, aryl, heteroaryl, heterocycloalkyl, arylaminocarbonyl, cycloalkylaminocarbonyl, or a saturated hydrocarbon fused ring system optionally having an aryl ring fused thereto, said ring system being optionally substituted with up to three alkyl groups on the alkyl or aryl rings thereof;

wherein any of said R_6 groups can be optionally substituted with up to 3 groups selected from $NR_{15}R_{16}$, alkyl, hydroxy, halogen, aryl, alkoxy, trihaloalkoxy, arylalkyloxy, NO_2, -SH, -S-alkyl, heteroarylcarbonyl, heteroaryl, alkylheteroaryl, or a moiety of formula -OC_2CH_2-O- attached to adjacent atoms of said R_6 group;

R_7 is heteroaryl or heterocycloalkyl;

R_8 is aryl;

R_9 and R_{10} are each independently alkylene having from 1 to about 20 carbons;

X is –N(R_{12})-, -C(R_{13})(R_{14})- or O;

R_{11} is H, heterocycloaryl or alkoxy, wherein said heterocycloaryl or alkoxy group can be optionally substituted with up to four groups independently selected from

halogen, amino, trihaloalkyl, alkoxycarbonyl, and CN;

R_{12} is H or C_1-C_6 alkyl; and

R_{13} and R_{14} are each independently H or C_1-C_6 alkyl;

R_{15} is H, halogen, C_{1-12} alkyl, methylcarbonyl, heterocycloalkyl, arylsulfonyl, heteroarylalkyl, aminoalkyl, arylcarbonyl, branched and straight chain polyaminoalkyl, or a group of formula $CH_2(CHOH)_4CH_2OH$,

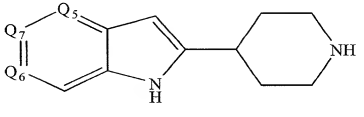
wherein said methylcarbonyl, heterocycloalkyl, arylsulfonyl, heteroarylalkyl, aminoalkyl, arylcarbonyl, and branched and straight chain polyaminoalkyl groups can be substituted by up to 3 OH groups;

R_{16} is H, halogen, or C_1-C_6 alkyl;

or R_{15} and R_{16} together with the nitrogen atom to which they are attached can form a succinimicdo or phthalimido group or a fused ring derivative thereof, wherein said succinimido or phthalimido group or fused ring derivative thereof can be optionally substituted by up to three substituents independently selected from NO_2 and halogen, or a group of Formula I at position R_1 threreof;

or R_{15} and R_{16} together with the nitrogen atom to which they are attached can form a group of Formula I wherein said nitrogen atom is Q_4 thereof;

Also provided by the present invention are compounds of Formula:



wherein:

Q_5 is CH or N;

Q_6 is C-R_{61} or N;

Q_7 is C-R_{60} or N;

R_{60} and R_{61} are each independently H, halogen, C_{1-6} alkyl, trihaloalkyl, or C_{1-6} alkoxy;

provided that when Q_6 is C-R_{61}, Q_7 is C-R_{60} and Q_5 is CH, then R_{60} and R_{61} are not both H.

The present invention provides methods for treating a patient having a bacterial infection comprising administering to said patient a compound of the invention. Preferably, said patient is a human. Also provided are methods for inhibiting bacterial growth comprising contacting a bacterium with a compound of the invention. In some preferred embodiments, said bacterium a gram-positive bacteria, preferably from among staphylococci, enterococci, and streptococci. In some embodiments the bacterium is S. aureus, E. hirae, S. pyogenes, S. pneumoniae, E. coli, P. vulgaris, K. pneumoniae, P. aeruginosa, C. albicans, E.faecalis, E.faecali, or E.faecium.

The present invention also provides compositions that include at least one compound of the invention.

Brief Description of the Drawings

Figure 1 is a table showing activity of benzimidazoles of Examples 11 and 12 against four strains of Gram positive and four strains of gram negative bacteria.

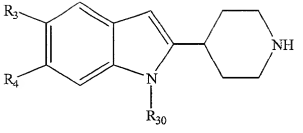
Figure 2 is a table showing activity of benzimidazoles of Examples 11 and 12 against seven clinically important strains of entercocccus.

Figure 3 shows the in vitro inhibitorial activity of selected benzimidazoles of Example 16 against four Gram positive bacterial strains, four gram negative bacterial strains and one yeast strain.

Detailed Description

The present invention also provides compositions containing the subject compounds, and methods for using the subject compounds. Methodologies for making the compounds of the invention are also disclosed. Other useful methodologies will be apparent to those skilled in the art, once armed with the present disclosure. These and other features of the compounds of the subject invention are set forth in more detail below.

In some embodiments, compounds are provided having the formula:

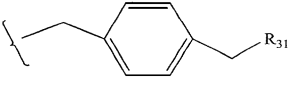


wherein:

R_3 and R_4 are independently each H, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, trihaloalkyl, alkoxycarbonyl, alkoxy, $NR_{15}R_{16}$, or NO_2;

R_{30} is C_{1-6} alkyl, heteroarylalkyl, arylalkyl, or heteroaryl, wherein each of said heteroarylalkyl, arylalkyl, or heteroaryl groups each can be optionally substituted with up to three substitutents selected from haloegn, NO_2, and mono-, di-, or trihaloalkyl;

or R_{30} has the structure XX:



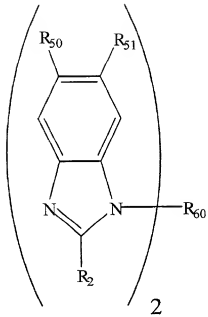
XX

wherein R_{31} is alkylamino, aminoalkylamino, poly(alkylamino)amino, heterocycloalkylamino, heterocycloalkyl, -NH-$(CHOH)_4$-CH_2OH, -NH-$(CH_2)_{1-12}$-heteroaryl or -NH-$(CH_2)_{1-12}$-heterocycloalkyl.

In some embodiments, R_{30} has the structure XX. In some such embodiments, R_{31} has the structure of any of the radicals shown in Example 11, designated for compounds 7a-x, *infra*.

In further embodiments, R_1 is pyridin-4-yl-methyl, pyridin-3yl-methyl, 4-fluorophen-1-yl-methyl, 4-nitrophen-1-yl-methyl, 4-(bromomethyl)phen-1-yl-methyl, pyrimidine-2-yl, or 2,4-dinitrophen-1-yl.

In a further aspect, the present invention provides dimeric benzimidazole compounds having the structure:



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wherein:

R_2 is NH_2 or piperidin-4-yl;

R_{50} and R_{51} are each independently selected from H, halogen, C_1-C_6 alkyl, trihaloalkyl, alkoxycarbonyl, alkoxy, $NR_{15}R_{16}$, and NO_2, wherein said C_1-C_6 alkyl, alkoxycarbonyl, and alkoxy groups can each be optionally substituted with $NR_{15}R_{16}$;

R_{15} is H, halogen, C_1-$_{12}$ alkyl, methylcarbonyl, heterocycloalkyl, arylsulfonyl, heteroarylalkyl, aminoalkyl, arylcarbonyl, branched and straight chain polyaminoalkyl, or a group of formula $CH_2(CHOH)_4CH_2OH$,

wherein said methylcarbonyl, heterocycloalkyl, arylsulfonyl, heteroarylalkyl, aminoalkyl, arylcarbonyl, and branched and straight chain polyaminoalkyl groups can be substituted by up to 3 OH groups;

R_{16} is H, halogen, or C_1-C_6 alkyl;

or R_{15} and R_{16} together with the nitrogen atom to which they are attached can form a succinimicdo or phthalimido group or a fused ring derivative thereof, wherein said succinimido or phthalimido group or fused ring derivative thereof can be optionally substituted by up to three substituents independently selected from NO_2 and halogen;

R_{60} is alkylene having from 1 to 18 carbons, or $-R_9$-X-R_{10}-)H;

R_9 and R_{10} are each independently alkylene having from 1 to about 20 carbons;

X is $-N(R_{12})-$, $-C(R_{13})(R_{14})-$ or O; and

R_{12}, R_{13} and R_{14} are each independently H or C_1-C_6 alkyl.

In some embodiments if the dimeric compounds, R_2 is piperidin-4-yl. In further embodiments, R_{50} and R_{51} are each halogen, preferably chlorine.

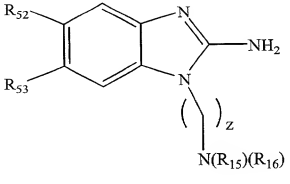
In some embodiments, R_{60} is alkylene having from 1 to 6 carbons or from 1 to 4 carbons. In some embodiments, R_{60} is $-CH_2-C_6H_4-CH_2-$, preferably where $-CH_2-C_6H_4-CH_2-$ is a para-α,α-xylene radical.

In some of the foregoing embodiments, R_2 is NH_2. I further embodiments, R_{50} and R_{51} are each independently selected from H, halogen, methyl, $COOCH_3$, CN and CF_3.

In some embodiments, R_{60} is $-R_9-X-R_{10}-$. In further embodiments, X is $-N(R_{12})-$. In some embodiments, R_{12} is methyl and R_9 and R_{10} are each $(CH_2)_2$ or $(CH_2)_3$, preferably wherein R_{50} and R_{51} are each halogen, or where R_{50} and R_{51} are each H, or where R_{50} is Br and R_{51} is H, or where R_{50} is CH_3 and R_{51} is H, or where $COOCH_3$ and R_{51} is H, or where CF_3 and R_{51} is H, or where R_{50} is CN and R_{51} is H.

In some embodiments, X is O. I some such embodiments, R_9 and R_{10} are each $(CH_2)_2$ or $(CH_2)_3$, preferably whereR_{50} and R_{51} are each halogen, or where R_{50} and R_{51} are each H, or where Br and R_{51} is H, or where R_{50} is CH_3 and R_{51} is H, or where R_{50} is $COOCH_3$ and R_{51} is H, or where R_{50} is CF_3 and R_{51} is H, or where R_{50} is CN and R_{51} is H.

In a further aspect, the present invention provides compounds of formula:



wherein:

R_{52} and R_{53} are each independently selected from H, halogen, C_1-C_6 alkyl, trihaloalkyl, alkoxycarbonyl, alkoxy, $NR_{15}R_{16}$, and NO_2, wherein said C_1-C_6 alkyl, alkoxycarbonyl, and alkoxy groups can each be optionally substituted with $NR_{15}R_{16}$;

R_{15} is H, halogen, C_{1-12} alkyl, methylcarbonyl, heterocycloalkyl, arylsulfonyl, heteroarylalkyl, aminoalkyl, arylcarbonyl, branched and straight chain polyaminoalkyl, or a group of formula $CH_2(CHOH)_4CH_2OH$;

wherein said methylcarbonyl, heterocycloalkyl, arylsulfonyl, heteroarylalkyl, aminoalkyl, arylcarbonyl, and branched and straight chain polyaminoalkyl groups can be substituted by up to 3 OH groups;

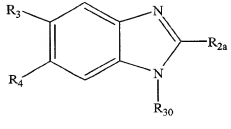
R_{16} is H, halogen, or C_1-C_6 alkyl;

or R_{15} and R_{16} together with the nitrogen atom to which they are attached can form a succinimicdo or phthalimido group or a fused ring derivative thereof, wherein said succinimido or phthalimido group or fused ring derivative thereof can be optionally substituted by up to three substituents independently selected from NO_2 and halogen; and z is 1 to 6.

In some embodiments, R_{15} and R_{16} are each methyl, preferably wherein z is 2 or 3, further preferably where R_{52} and R_{53} are each independently H, C_{1-6} alkyl, alkoxy optionally substituted with dialkylamino, or alkylamino. In further embodiments, R_{52} is H, preferably where R_{53} is methyl, methoxy, alkoxy optionally substituted with dialkylamino, or alkylamino, preferably wherein R_{53} is OCH_3 or $O(CH_2)_3N(CH_3)_2$.

In some embodiments, where R_{15} and R_{16} are each methyl, z is 2 or 3 and R_{52} is H, C_{1-6} alkyl, alkoxy optionally substituted with dialkylamino, or alkylamino, R_{53} is H. In some such embodiments, R_{52} is methyl, methoxy, alkoxy optionally substituted with dialkylamino, or alkylamino. In further embodiments, R_{52} is OCH_3 or $O(CH_2)_3N(CH_3)_2$.

Also privided by the present invention are compounds having the Formula:



wherein:

R_{2a} is amino, phenyl, mono- or bicyclic heterocycloalkyl having 1 or 2 ring nitrogen atoms, mono- or bicyclic heteroaryl having 1 or 2 ring nitrogen atoms, cycloalkyl, halogen, heterocycloalkylalkyl (i.e., alkyl sub w' heterocycloalkyl) having 1 or 2 ring nitrogen atoms, mono- or bicyclic heterocycloalkylamino having 1 or 2 ring nitrogen atoms or a group of formula -S-alkylene-L_1 where L_1 is mono- or bicyclic-heteroaryl having 1 or 2 ring nitrogen atoms;

wherein each of said amino, phenyl, heterocycloalkyl, heteroaryl, cycloalkyl, heterocycloalkylalkyl, or heterocycloalkylamino groups can be optionally substituted with a group selected from amino, OH, C_1-C_{12} alkyl, a structure of formula -C(=O)CH(NH_2)-L_2 where L_2 is the side chain of a naturally occurring alpha amino acid, –C(NH_2)=NH, C_1-C_{12} alkylcarbonyl, mono- or bicyclic heteroaryl having 1 or 2 ring nitrogen atoms, mono- or bicyclic heteroarylalkyl having 1 or 2 ring nitrogen atoms, or S-alkyl-heteroaryl where said heteroaryl is mono- or bicyclic having 1 or 2 ring nitrogen atoms; and

R_3 and R_4 are each independently halogen, amino, NO_2, CN, C_{1-6} alkoxy or C_{1-6} alkyl optionally substituted with up to 3 halogen atoms; and

R_{30} is H, alkyl, aryl, arylalkyl, heteroaryl; heteroarylalkyl, heterocycloalkyl, arylsulfonyl, aryloxycarbonyl, alkoxyalkoxyalkyl, alkyl-S-R_7, alkyl-NH-C(=O)-R_8 or –R_9-X-R_{10}-R_{11})H;

wherein each of the alkyl, aryl, arylalkyl heteroaryl, heteroarylalkyl, heterocycloalkyl, arylsulfonyl, aryloxycarbonyl and alkoxyalkoxyalkyl moieties in each of the foregoing R_1 groups can be optionally substituted with up to 3 groups independently selected from the group consisting of C_1-C_6 alkyl, OH, hydroxyalkyl, -C(=O)-R_5, CN, aryl, alkoxycarbonyl, alkylaryl, arylalkyl, heteroaryl, S-heteroaryl optionally substituted with halogen, heteroarylalkyl optionally substituted with halogen, heterocycloalkyl optionaly substituted with amino, NO_2, halogen, monohaloalkyl, dihaloalkyl, trihaloalkyl, perhaloaryl, perhaloalkylaryl, alkyl-$NR_{15}R_{16}$ and $NR_{15}R_{16}$;

or one of said alkyl, aryl, arylalkyl heteroaryl, heteroarylalkyl, heterocycloalkyl, arylsulfonyl, aryloxycarbonyl or alkoxyalkoxyalkyl moieties of one of said R_1 groups can be attached to a structure of Formula I at position R_1 thereof;

R_5 is H, –NHNHR_6, –NHN=CH-R_6, heteroaryl, heterocycloalkyl, wherein

said hereteroaryl group can be optionally substituted with an aryl or heteroaryl group,

R_6 is aryl, heteroaryl; arylsulfonyl, heteroarylsulfonyl, -C(=S)-NH-aryl, -C(=S)-NH-arylcarbonyl, -C(=S)-NH-heteroarylcarbonyl, -C(=S)-NH-alkylene-R_{21}, -C(=O)-NH-aryl, -C(=O)-NH-arylcarbonyl, -C(=O)-NH-heteroarylcarbonyl, or -C(=O)-NH-alkylene-R_{21} where R_{21} is carboxy, alkoxycarbonyl, aryl, heteroaryl, heterocycloalkyl, arylaminocarbonyl, cycloalkylaminocarbonyl, or a saturated hydrocarbon fused ring system optionally having an aryl ring fused thereto, said ring system being optionally substituted with up to three alkyl groups on the alkyl or aryl rings thereof;

wherein any of said R_6 groups can be optionally substituted with up to 3 groups selected from $NR_{15}R_{16}$, alkyl, hydroxy, halogen, aryl, alkoxy, trihaloalkoxy, arylalkyloxy, NO_2, -SH, -S-alkyl, heteroarylcarbonyl, heteroaryl, alkylheteroaryl, or a moiety of formula $-OC_2CH_2-O-$ attached to adjacent atoms of said R_6 group;

R_7 is heteroaryl or heterocycloalkyl;

R_8 is aryl;

R_9 and R_{10} are each independently alkylene having from 1 to about 20 carbons;

X is $-N(R_{12})-$, $-C(R_{13})(R_{14})-$ or O;

R_{11} is H, heterocycloaryl or alkoxy, wherein said heterocycloaryl or alkoxy group can be optionally substituted with up to four groups independently selected from halogen, amino, trihaloalkyl, alkoxycarbonyl, and CN;

R_{12} is H or C_1-C_6 alkyl; and

R_{13} and R_{14} are each independently H or C_1-C_6 alkyl;

R_{15} is H, halogen, C_{1-12} alkyl, methylcarbonyl, heterocycloalkyl, arylsulfonyl, heteroarylalkyl, aminoalkyl, arylcarbonyl, branched and straight chain polyaminoalkyl, or a group of formula $CH_2(CHOH)_4CH_2OH$,

wherein said methylcarbonyl, heterocycloalkyl, arylsulfonyl, heteroarylalkyl, aminoalkyl, arylcarbonyl, and branched and straight chain polyaminoalkyl groups can be substituted by up to 3 OH groups;

R_{16} is H, halogen, or C_1-C_6 alkyl;

or R_{15} and R_{16} together with the nitrogen atom to which they are attached can form a succinimicdo or phthalimido group or a fused ring derivative thereof, wherein

said succinimido or phthalimido group or fused ring derivative thereof can be optionally substituted by up to three substituents independently selected from NO_2 and halogen, or a group of Formula I at position R_1 threreof;

or R_{15} and R_{16} together with the nitrogen atom to which they are attached can form a group of Formula I wherein said nitrogen atom is Q_4 thereof;

In some such embodiments, R_3 and R_4 are each halogen, preferably chlorine. In further embodiments, R_{2a} is amino, Cl, phenyl, monocyclic heterocycloalkyl having 1 or 2 ring nitrogen atoms, monocyclic heteroaryl having 1 ring nitrogen atom, cyclopenyl, cyclohexyl, heterocycloalkyl-methyl, piperidine-4-yl amino or a group of formula -S-(C_{2-4} alkylene)-N-phthalimido; wherein each of said phenyl, heterocycloalkyl heteroaryl, cyclopenyl, cyclohexyl, heterocycloalkyl-methyl, and piperidine-4-yl amino groups can be optionally substituted with a group selected from NH_2, OH, CH_3, $COOCH_3$, a structure of formula -C(=O)CH(NH_2)-L_2 where L_2 is a serine or threonine side chain, –C(NH_2)=NH, benzimidazolyl, or benzimidazolemethylyl.

In further embodiments, R_{2a} is amino, Cl, piperidinyl, pyridinyl, phenyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, -CH_2-piperazinyl, piperidine-4-yl-amino or S-alkyl-phthalyl, wherein said piperidinyl, pyridinyl, phenyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, -CH_2-piperazinyl, or S-alkyl-phthalyl groups can be optionally substituted with a group selected from NH_2, methylcarbonyl, -C(=O)CH(NH_2)-CH_2OH, methyl, OH, –C(NH_2)=NH, OH, benzimidazole-2-yl, and -CH_2-benzimidazole-2-yl.

In still further embodiments, R_{2a} is amino, Cl, piperidinyl, pyridinyl, phenyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, -CH_2-piperazinyl, piperidine-4-yl-amino or S-alkyl-phthalyl, wherein said piperidinyl, pyridinyl, phenyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperazinyl, -CH_2-piperazinyl, or S-alkyl-phthalyl groups can be optionally substituted with a group selected from NH_2, methylcarbonyl, -C(=O)CH(NH_2)-CH_2OH, methyl, OH, –C(NH_2)=NH, OH, benzimidazole-2-yl, and -CH_2-benzimidazole-2-yl.

In further embodiments, R_{2a} is amino, Cl, pyridin-4-yl, phenyl substituted with amino, cyclopentyl substituted with amino, cyclohexyl optionally substituted with amino, pyrrolidin-2-yl optionally substituted by hydroxy, piperazin-1-yl optionally substituted at the 4-yl position by benzimidazole-2-yl, piperazin-1-yl-methyl optionally substituted at the 4-yl position by -CH_2-benzimidazole-2-yl, piperidine-4-yl-amino,

piperidin-1-yl substituted by amino, S-alkyl-phthalyl, or said R_2 is piperidin-4-yl optionally substituted at the 1-yl position with -C(=O)CH_3, -C(=O)CH(NH_2)-CH_2OH, –C(NH_2)=NH, or CH_3.

In still further embodiments, R_{2a} is amino, piperidin-4-yl-amino, piperiazine-1-yl optionally substituted with benzimidazole-2-yl, pyridin-4-yl, piperidin-4-yl optionally substituted at the 1-yl position with -C(=O)CH_3, -C(=O)CH(NH_2)-CH_2OH, –C(NH_2)=NH, or CH_3, 4-amino-piperdin-1-yl, 3-amino-phen-1-yl, 3-amino-cyclopent-1-yl, cyclohexyl optionally substituted at the 3-yl or 4-yl position with NH_2, 4-hydroxypyrrolidin-2-yl, piperazin-1-yl-methyl, 4-(benzimidazole-2-yl-methyl)piperazin-1-yl-methyl, or S-alkyl-phthalyl where said alkyl has from 2 to 4 carbons.

In still further embodiments, R_{2a} is piperidin-4-yl optionally substituted at the 1-yl position with -C(=O)CH_3, -C(=O)CH(NH_2)-CH_2OH, –C(NH_2)=NH, or CH_3.

In further embodiments where R_3 and R_4 are each chlorine, R_{2a} is piperidin-4-yl optionally substituted at the 1-yl position with -C(=O)CH_3, -C(=O)CH(NH_2)-CH_2OH, –C(NH_2)=NH, or CH_3.

In some embodiments, R_{2a} is piperidin-4-yl, and, preferably R_3 and R_4 are each chlorine. In some embodiments, R_{2a} is NH_2, preferably wherein R_3 and R_4 are each chlorine.

In some embodiments where R_3 and R_4 are each chlorine and R_{2a} is piperidin-4-yl, R_{30} is alkyl substituted with -C(=O)-R_5, preferably wherein R_5 is –NHNHR_6, or –NHN=CH-R_6.

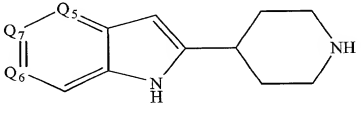
In some such embodiments, R_5 is –NHNHR_6 where R_6 is -C(=O)-NH-aryl, -C(=O)-NH-cycloalkyl, -C(=S)-NH-aryl, arylsulfonyl, heteroarylsulfonyl, heterocycloalkyl, arylaminocarbonyl, cycloalkylaminocarbonyl, -C(=S)-NH-alkylene-R_{21} where R_{21} is heteroaryl or heterocycloaryl, or a saturated hydrocarbon fused ring system optionally having an aryl ring fused thereto, said ring system being optionally substituted with up to three alkyl groups on the alkyl or aryl rings thereof;
wherein any of said R_6 groups can be optionally substituted with up to 3 groups selected from $NR_{15}R_{16}$, NO_2, a moiety of formula -OC_2CH_2-O- attached to adjacent atoms of said R_6 group, aryl, C_{1-6} alkoxy, carboxy, or C_{1-6} trihaloalkoxy.

In some embodiments, R_5 is –NHN=CH-R_6. In some such embodiments, R_6 is aryl or heteroaryl optionally substituted with up to 3 groups selected from OH, C_{1-6}

alkoxy, NO_2, C_{1-6} trihaloalkoxy, C_{1-6} trihaloalkyl, aryl, arylalkyloxy, and a moiety of formula $-OC_2CH_2-O-$ attached to adjacent atoms of said R_6 group.

In some embodiments wherein R_{2a} is piperidin-4-yl, R_{30} has the formula $-(CH_2)_q-L_4$ where q is 0 to 6 and L_4 is aryl, heteroaryl or heterocycloalkyl, arylsulfonamino, arylcarboxyamino or -S-heteroaryl, where each of said L_4 is optionally substituted with up to three substituents selected from halogen and NO_2. Preferably, said L_4 is maleimido, succinimido, phthalimido, naphthalimido, pyromellitic diimido, phenylsulfonamido, phenylcarboxamido, benzopyrrolidine, benzimidazole, triazole, or -S-benzimidazole.

Also provided by the present invention are compounds of Formula:



wherein:

Q_5 is CH or N;

Q_6 is C-R_{61} or N;

Q_7 is C-R_{60} or N;

R_{60} and R_{61} are each independently H, halogen, C_{1-6} alkyl, trihaloalkyl, or C_{1-6} alkoxy; provided that when Q_6 is C-R_{61}, Q_7 is C-R_{60} and Q_5 is CH, then R_{60} and R_{61} are not both H.

In some embodiments, Q_5 is N. In further embodiments, Q_6 is N.

In some embodiments, Q_7 is N. In further embodiments, Q_5 is N, Q_6 is C-R_{61} and Q_7 is C-R_{60}. In further embodiments, Q_7 is N, Q_6 is C-R_{61} and Q_5 is CH. In further embodiments, Q_5 is N, Q_6 is N and Q_7 is C-R_{60}. In further embodiments, Q_5 is CH, Q_6 is R_{61} and Q_7 is C-R_{60}.

In some embodiments where Q_5 is CH, Q_6 is R_{61} and Q_7 is C-R_{60}, R_{60} and R_{61} are each independently H, Br, Cl, methoxy, methyl or trifluoromethyl. In further such embodiments, R_{60} is OCH_3 and R_{61} is H, or R_{60} is CH_3 and R_{61} is H, or R_{60} is Br and R_{61} is H, or R_{60} is Cl and R_{61} is H, or R_{60} is CF_3 and R_{61} is H, or R_{60} is Cl and R_{61} is CH_3, or R_{60} and R_{61} are both Cl.

The present invention provides methods for treating a patient having a

bacterial infection comprising administering to said patient a compound of claim 1. Preferably, said patient is a human. Also provided are methods for inhibiting bacterial growth comprising contacting a bacterium with a compound of the invention. In some preferred embodiments, said bacterium is S. aureus, E. hirae, S. pyogenes, S. pneumoniae, E. coli, P. vulgaris, K. pneumoniae, P. aeruginosa, C. albicans, E.faecalis, E.faecali, or E.faecium.

The present invention also provides compositions that include at least one compound of the invention.

As used herein the term alkyl is intended to have it accustomed meaning of a straight or branched chain hydrocarbon, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, n-pentyl, sec-pentyl, t-pentyl, neopentyl, and the like.

As used herein the term aryl is intended to mean an aromatic hydrocarbon system for example phenyl, naphthyl, phenanthrenyl, anthracenyl, pyrenyl, and the like. In some embodiments, aryl groups have from 6 to 10 carbon atoms.

As used herein, the term arylalkyl (or "aralkyl") is intended to mean an alkyl group that has an aryl group appended thereto, for example benzyl and naphthylmethyl groups. In some embodiments, arylalkyl groups have from 7 to 11 carbon atoms.

As used herein, the term alkylaryl (or "alkaryl") is intended to mean an aryl group that has one or more alkyl groups appended thereto, for example a 4-methylphen-1-yl group, or a xylyl group attached through the phenyl ring thereof.

As used herein, the term heteroaryl means an aryl group that contains one or more ring hetero (i.e., non-carbon) atoms, which are preferably O, N or S, more preferably N. In some embodiments, heteroaryl groups are monocyclic or bicyclic, and have up to four ring nitrogen atoms. Examples of some preferred heteroaryl groups include radicals derived from pyrrole, pyrazole, imidazole, triazoles, tetrazole, pyridine, pyrazine, pyridazine, pyrimidine, triazines, quinolines, indoles, benzimidazoles, and the like.

As used herein, the term heteroarylalkyl is intended to mean an alkylene group that has a heteroaryl group appended thereto, for example a group of formula $-CH_2-$ benzimidazol-2-yl.

As used herein, the term cycloalkyl refers to nonaromatic hydrocarbon ring systems, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, including multiple

ring systems such as decahydronaphthalene and adamantane. Cycloalkyl groups can also include points of unsaturation, and therefor also include cyclopentenyl, and cyclohexenyl groups.

As used herein, the term heterocycloalkyl is intended to mean a group that contains a nonaromatic ring which contains one or more ring hetero (i.e., non-carbon) atoms which are preferably O, N or S, more preferably N. Also included in the definition of heterocycloalkyl are moieties that contain exocyclic heteroatoms, for example a cycloalkyl ring having a ring carbon attached to an exocyclic O or S atom through a double bond. Also included in the definition of heterocycloalkyl are moieties that having one or more aromatic rings fused (i.e., having a bond in common with) to the nonaromatic heterocyclic ring, for example phthalimidyl, naphthalimidyl pyromellitic diimidyl, phthalanyl, and benzo derivatives of saturated heterocycles such as indolene and isoindolene groups.

As used herein, the term arylsulfonyl is intended to mean a moiety of formula $-S(=O)_2$-aryl, for example phenylsulfonyl. The term heteroarylsulfonyl means a moiety of formula $-S(=O)_2$-heteroaryl, for example pyridinesulfonyl.

As used herein the term aryloxy is intended to mean an aryl group attached through an oxygen atom, for example phenoxy.

As used herein, the term aryloxycarbonyl is intended to men a moiety of formula -C(=O)-O-aryl, for example phenoxycarbonyl.

As used herein, the term alkoxyalkoxyalkyl is intended to mean a moiety of formula -alkylene-O-alkylene-O-alkyl.

As used herein, the term hydroxyalkyl is intended to mean an alkyl group that has a hydrogen atom thereof replaced with OH.

As used herein, the term alkoxycarbonyl is intended to mean a moiety of formula -C(=O)-O-alkyl.

As used herein, the term amino refers to NH_2. The term halogen includes F, Cl, Br and I. The prefix "halo" is intended to denote a halogen atom. The term "perhalo" is intended to refer to the substitution of all hydrogen atoms for halogen atoms. Thus, the term "perhaloaryl" indicated a fully halogenated moiety, for example a pentafouorophenyl radical, and the term "perhaloalkylaryl" would be understood to indicate a full halogenated alkylaryl group, for example a 2,3,5,6, tetrafluoro-4-trifluoromethyl-phenyl radical.

In one aspect, the present invention provides dimeric compounds wherein two benzimidazole core structures are joined, preferably at the 1-position, by a tether. Thus, in certain embodiments, various moieties appended to the 1-position of the benzimidazole core can be appended to a benzimidazole core structure at the 1-position thereof.

As used herein, the term alkoxy means moieties of formula -O-alkyl. The term arylcarbonyl means a moiety of formula -C(=O)-aryl. The term heteroarylcarbonyl means a moiety of formula -C(=O)-heteroaryl.

The term arylaminocarbonyl means a moiety of formula -C(=O)-NH-aryl. The term cycloalkylaminocarbonyl means a moiety of formula -C(=O)-NH-cycloalkyl.

The phrase "saturated hydrocarbon fused ring system optionally having an aryl ring fused thereto" is intended to denote saturated hydrocarbon ring systems having up to three fused rings, for example decalin, which can optionally have an aryl ring fused thereto, for example benzo derivatives of cycloalkyl groups.

The term arylalkyloxy denotes a froup of formula -O-alkyl-aryl, for example a benzyloxy group. The term alkylheteroaryl denotes a group of formula -heteroaryl-alkyl, for example a 4-methyl-pyrid-2-yl group.

The phrase "moiety of formula $-OCH_2CH_2-O-$ attached to adjacent atoms of" is intended to mean that the $-OCH_2CH_2-O-$ oxygen atoms are attached to adjacent atoms an indicated moiety (which preferably is a cyclic group) to form a 6 membered fused ring comprising the $-OCH_2CH_2-O-$ group and the two atoms to which it is attached.

The term methylcarbonyl is intended to denote an acetoyl (i.e., $CH_3C(=O)-$) group. The term aminoalkyl denotes a group of formula -alkyl-NH_2.

The phrase "branched and straight chain polyaminoalkyl" is intended to mean a group of formula $-((CH_2)_n-NH)_m-H$ wherein n can be from 1 to 6 and m can be from 2 to about 12, in any one or more of the hydrogens attached to nitrogen can be replaced with a group of formula $-((CH_2)_p-NH)_q-H$ where p is 1 to 6 and q is 1 to 12.

In some embodiments, compounds of the invention contain simple polyalchol moieties of formula $-CH_2(CHOH)_4CH_2OH$. It is intended that each such group specifically include each individual stereoisomer of such formula, as well as racemic forms of the same.

In certain embodiments, variables R_{15} and R_{16} together with the nitrogen

atom to which they are attached can form a nitrogen heterocycle which can be aromatic or aliphatic, or aliphatic having one or more aromatic rings fused thereto (i.e., a fused ring derivative). Thus, in some embodiments, R_{15} and R_{16} together with the nitrogen atom to which they are attached can form, for example, an N-maleimidyl, N-succinimidyl, N-phthalimidyl, N-naphthalimidyl, N-pyromellitic diimidyl, N-benzopyrrolidinyl, or benzimidazol-1-yl group.

The term alkylamino is intended to denote a group of formula -NH-alkyl. The term aminoalkylamino is intended to denote a group of formula -NH-alkyl-NH_2. The term poly(aminoalkyl)amino is intended to denote a group of formula -NH-(alkyl-$NH)_x$-H where x is from 2 to about 12, and wherein any one or more of the hydrogens attached to nitrogen can be replaced with a group of formula -$((CH_2)_p$-$NH)_q$-H where p is 1 to 6 and q is 1 to 12.

The term heterocycloalkylamino is intended to denote a group of formula -NH-heterocycloalkyl. The term heterocycloalkylalkyl is intended to denote a group of formula alkyl-heterocycloalkyl).

The term "side chain of a naturally occurring alpha amino acid" is intended to mean the side chain of naturally occurring alpha amino acids, with the exception of glycnie, that are known to have the formula H_2N-CHR-COOH, where R is the side chain. Examples of such naturally occurring amino acids include the 20 so called "essential" amino acids, for example serine and threonine. Further side chains of naturally occurring alpha amino acids can be found in Bikochemistry, 3rd Edition, Matthews, Van Holde, and Ahern, Addison Wesley Longman, San Francisco, CA, incorporated by reference herein in its entirety.

As used herein, the term alkoxyalkoxyalkyl is intended to denote a group of formula alkyl-O-alkyl-O-alkyl. The term hydroxyalkyl is intended to mean a hydroxy group that is substituted with up to 3 hydroxy groups. The term heteroarylcarbonyl denotes a moiety of formula -C(=O)-heteroaryl. The term arylaminocarbonyl denotes a moiety of formula -C(=O)-NH-aryl. The term cycloalkylaminocarbonyl denotes a moiety of formula -C(=O)-NH-cycloalkyl.

The compounds of the present invention and their pharmaceutically acceptable salts are useful in for the treatment of bacterial infections in animal and human subjects. The compounds of the invention can be used alone, or in a pharmaceutical

composition containing one or more compounds of the invention, in combination with one or more pharmaceutically acceptable carriers. Thus, in further aspects, the present invention includes pharmaceutical compositions and methods of treating bacterial infections utilizing as an active ingredient the novel compounds described herein.

In some embodiments, the compounds of the invention can be prepared as amine salts, which can contain any of a variety of pharmaceutically acceptable counterions. Suitable counterions include acetate, adipate, aminosalicylate, anhydromethylenecitrate, ascorbate, aspartate, benzoate, benzenesulfonate, bromide, citrate, camphorate, camphorsulfonate, chloride, estolate, ethanesulfonate, fumarate, glucoheptanoate, gluconate, glutamate, lactobionate, malate, maleate, mandelate, methanesulfonate, pantothenate, pectinate, phosphate/diphosphate, polygalacturonate, propionate, salicylate, stearate, succinate, sulfate, tartrate and tosylate. Other suitable anionic species will be apparent to the skilled practitioner.

Representative examples of compounds of the invention are shown below. It is contemplated that the present invention include all possible protonated and unprotonated forms of the compounds disclosed herein.

The compounds of the invention can be formulated in pharmaceutical compositions which can include one or more compounds of the invention and one or more pharmaceutically acceptable carriers. The compounds of the invention can be administered in powder or crystalline form, in liquid solution, or in suspension. They may be administered by a variety of means known to be efficacious for the administration of antibiotics, including without limitation topically, orally and parenterally by injection (e.g., intravenously or intramuscularly).

When administered by injection, a preferred route of delivery for compounds of the invention is a unit dosage form in ampules, or in multidose containers. The injectable compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain various formulating agents. Alternatively, the active ingredient may be in powder (lyophillized or non-lyophillized) form for reconstitution at the time of delivery with a suitable vehicle, such as sterile water. In injectable compositions, the carrier is typically comprised of sterile water, saline or another injectable liquid, e.g., peanut oil for intramuscular injections. Also, various buffering agents, preservatives and the like can be included.

Topical applications may be formulated in carriers such as hydrophobic or hydrophilic bases to form ointments, creams, lotions, in aqueous, oleaginous or alcoholic liquids to form paints or in dry diluents to form powders.

Oral compositions may take such forms as tablets, capsules, oral suspensions and oral solutions. The oral compositions may utilize carriers such as conventional formulating agents, and may include sustained release properties as well as rapid delivery forms.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated, the route and frequency of administration, the sensitivity of the pathogen to the particular compound selected, the virulence of the infection and other factors. Such matters, however, are left to the routine discretion of the physician according to principles of treatment well known in the antibacterial arts. Another factor influencing the precise dosage regimen, apart from the nature of the infection and peculiar identity of the individual being treated, is the molecular weight of the compound.

The compositions for human delivery per unit dosage, whether liquid or solid, may contain from about 0.01% to as high as about 99% of active material, the preferred range being from about 10-60%. The composition will generally contain from about 15 mg to about 2.5 g of the active ingredient; however, in general, it is preferable to employ dosage amounts in the range of from about 250 mg to 1000 mg. In parenteral administration, the unit dosage will typically include the pure compound in sterile water solution or in the form of a soluble powder intended for solution, which can be adjusted to neutral pH and isotonic.

The invention described herein also includes a method of treating a bacterial infection in a mammal in need of such treatment comprising administering to said mammal a compound of the invention in an amount effective to treat said infection. One preferred method of administration of the antibacterial compounds of the invention include oral and parenteral, e.g., i.v. infusion, i.v. bolus and i.m. injection.

Compounds provided herein can be formulated into pharmaceutical compositions by admixture with pharmaceutically acceptable nontoxic excipients and carriers. As noted above, such compositions may be prepared for use in parenteral administration, particularly in the form of liquid solutions or suspensions; or oral administration, particularly in the form of tablets or capsules; or intranasally, particularly

in the form of powders, nasal drops, or aerosols; or dermally, via, for example, transdermal patches; or prepared in other suitable fashions for these and other forms of administration as will be apparent to those skilled in the art.

The composition may conveniently be administered in unit dosage form and may be prepared by any of the methods well known in the pharmaceutical art, for example, as described in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., Easton, PA, 1980). Formulations for parenteral administration may contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils and vegetable origin, hydrogenated naphthalenes and the like. In particular, biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be useful excipients to control the release of the active compounds. Other potentially useful parenteral delivery systems for these active compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration contain as excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Formulations for parenteral administration may also include glycocholate for buccal administration, a salicylate for rectal administration, or citric acid for vaginal administration. Formulations for transdermal patches are preferably lipophilic emulsions.

The materials of this invention can be employed as the sole active agent in a pharmaceutical or can be used in combination with other active ingredients, e.g., other growth factors which could facilitate neuronal survival or axonal regeneration in diseases or disorders.

The concentrations of the compounds described herein in a therapeutic composition will vary depending upon a number of factors, including the dosage of the drug to be administered, the chemical characteristics (e.g., hydrophobicity) of the compounds employed, and the route of administration. In general terms, the compounds of this invention may be provided in effective inhibitory amounts in an aqueous physiological buffer solution containing about 0.1 to 10% w/v compound for parenteral administration. Typical dose ranges are from about 1 mg/kg to about 1 g/kg of body weight per day; a preferred dose range is from about 0.01 mg/kg to 100 mg/kg of body weight per day. Such

formulations typically provide inhibitory amounts of the compound of the invention. The preferred dosage of drug to be administered is likely, however, to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, and formulation of the compound excipient, and its route of administration.

As used herein, the term "contacting" means directly or indirectly causing at least two moieties to come into physical association with each other. Contacting thus includes physical acts such as placing the moieties together in a container, or administering moieties to a patient. Thus, for example administering a compound of the invention to a human patient evidencing a disease or disorder associated with abnormal and/or aberrant activity of such proteases falls within the scope of the definition of the term "contacting".

Compounds of the invention also are useful for in silico studies to determine potential binding to binding pockets present in a variety of bacteria, including those disclosed in the Examples herein. Thus, the present invention further provides methods for determining binding affinities for classes of compounds in silico. In the methods, representations of the compounds of the invention can be used in molecular modeling studies to determine such binding affinities, and therefore aid in the design of therapeutics.

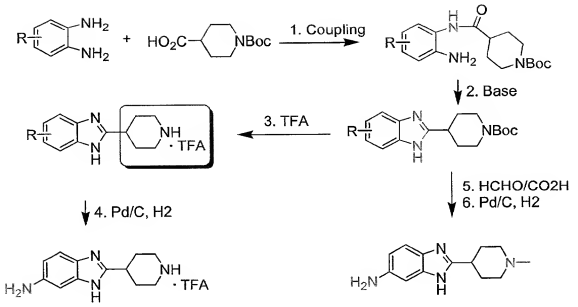
While the present invention has been described with specificity in accordance with certain of its preferred embodiments, the following examples serve only to illustrate the invention and are not intended to limit the same.

Examples:

Example 1

General Procedure for Preparation of Benzimidazoles Having Modification to the Phenyl (B) Ring

The general procedure for preparation of benzimidazoles having modification to the phenyl (B) ring is shown in Scheme 1, below:



Scheme 1

Generally, the steps of the synthesis are:

(1) N-Boc isonipecotic acid (25 g, 109 mmol) was dissolved in DMF (500 mL). HATU (49.5 g, 130 mmol) was added, followed by DMAP (16.0 g, 150 mmol) and DIEA (45 mL, 260 mmol). After the mixture was stirred for 30 minutes, diamine (105 mmol) was added and the resulting reaction mixture stirred overnight. The mixture was concentrated to one fourth of the volume, and poured into brine, extracted with dichloromethane (3X150 mL). The combined organic solution was dried over magnesium sulfate and concentrated too give black oil.

(2) The black oil was dissolved in ethanol (250 mL) and 2 M sodium hydroxide (250 mL). The mixture was refluxed overnight, cooled to room temperature and poured into saturated citric acid solution. The resulting mixture was extracted with dichloromethane (4X150 mL), and the combined organic solution was dried over magnesium sulfate and concentrated too give a black oil, which was purified on silica gel with ethyl acetate and dichloromethane to give the desired product.

(3) N-Boc compound (0.02 mmol) was placed in a 2-drum vial with a stirbar, and hydrochloric acid in dioxane (6.0 M, 500 L) was added. The mixture was stirred at room temperature for 30 minutes to give the corresponding product as precipitate (hydrochloride salt). The mixture was centrifuged, the solution removed using a pipette, and the solid salt was dried under vacuum overnight.

(4) 4-Nitro Benzimidazole hydrochloride salt (0.02 mmol), prepared by the procedure above was dissolved in methanol (2.0 mL), followed by the addition of palladium on carbon (10%, 5 mg). The resulting mixture was hydrogenated with a hydrogen balloon at room temperature for two hours. The catalyst was filtered off and washed with methanol (3X1.0 mL). The combined methanol solution was concentrated and dried under vacuum overnight.

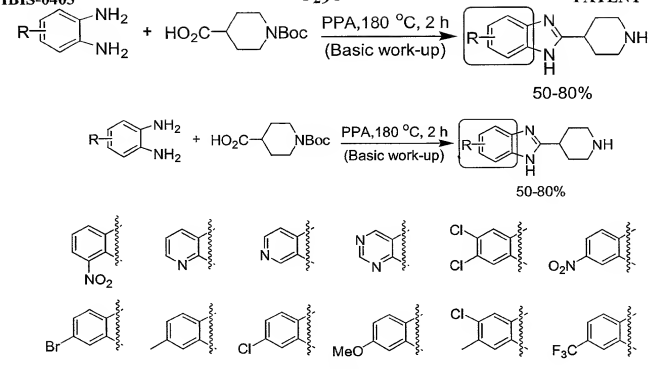
(5) N-Boc benzimidazole (0.04 mmol) was dissolved in formic acid (1.0 mL) and formaldehyde (1.0 mL, 37%), and the mixture was heated at 120 °C with an oil bath for 3 hours. Ethyl acetate (5.0 mL) was added, followed by excess solid sodium bicarbonate to neutralize the acid. The mixture was extracted with ethyl acetate (4X5 mL), and the combined organic solution was dried over magnesium sulfate and concentrated too give the crude product, which was purified on silica gel with methanol in chloroform (5%, 10% and 20%, 20%) and 2% $NH_3 \cdot H_2O$ and 20% MeOH in $CHCl_3$. (1694-5)
^1H NMR (200 MHz, $CDCl_3$): 8.44 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 7.56 (d, J = 9.0 Hz, 1H) 3.60-3.40 (m, 1H), 3.20-2.90 (m, 2.H), 2.35 (s, 3H), 2.30-2.00 (m, 5H)
LC/MS: $M+H^+ = 261$

(6) 4-Nitro Benzimidazole from step (4) (0.02 mmol) was dissolved in methanol (2.0 mL), followed by the addition of palladium on carbon (10%, 5 mg). The resulting mixture was hydrogenated with a hydrogen balloon at room temperature for two hours. The catalyst was filtered off and washed with methanol (3X1.0 mL). The combined methanol solution was concentrated and dried under vacuum overnight.

Example 2

General Procedure for Synthesis of Benzimidazoles Having Modification to the Imidazole (A) Ring

The general procedure for preparation of benzimidazoles having modification to the imidazole (A) ring is shown in Schemes 2 and 3, below:



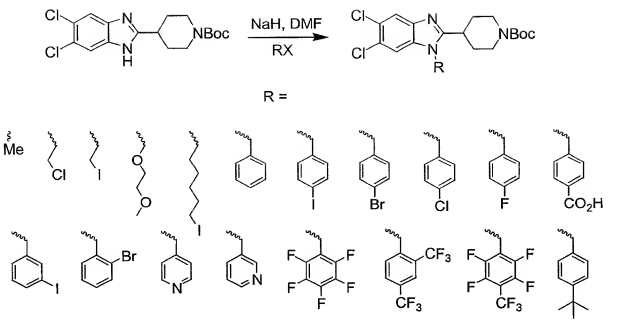
Scheme 2

Aryl diamines (1.0 mmol) and isonipecotic acid (129 mg, 1.2 mmol) were grounded into powder and well mixed. Polyphosphoric acid (PPA, 1.0 g) was then added. The mixture was heated in an oil-bath at 180 °C for two hours. The syrup was cooled to room temperature, and saturated sodium hydroxide was added to make the resulting mixture basic. The mixture was extracted with 30% isopropanol in chloroform (5 X 30 mL), and the combined organic solution was dried over magnesium sulfate and concentrated. The crude product was then purified by silica gel chromatography using methanol in chloroform (5%, 10% and 15%).

Rf = 0.15 (2% $NH_3 \cdot H_2O$ and 20% ^iPrOH in $CHCl_3$)

LC/MS: $M+H^+ = 202$ (2G column)

^1H NMR (200 MHz, $CDCl_3$): 7.55-7.44 (m, 2 H), 7.23-7.13 (m 2H), 3.34-2.98 (m, 3H), 2.83-2.66 (m, 2H), 2.14-2.00 (m, 2H), 1.96-1.72 (m, 2H).



Scheme 3

(1) Sodium hydride (24 mg, 60%, 1 mmol) was washed with hexane (3 X 1 mL). Anhydrous CH_3CN (2.0 mL) was added, followed by N-Boc-4,5-dichlorobenzimidazole (37 mg, 0.1 mmol) portion wise under argon. After the slurry was stirred at room temperature for 30 minutes, the alkylating halide (0.15 mmol) was added, and the reaction mixture was stirred at room temperature for another 30 minutes (The reaction progress was monitored by TLC). The reaction was cooled with an ice bath, and ice water (2.0 mL) was carefully added. The resulting crude mixture was extracted with ethyl acetate (3 X 10 mL), the combined organic solution was washed with brine (2 X 2 mL) and dried over magnesium sulfate and concentrated. The crude product was then purified by silica gel chromatography using ethyl acetate in hexane (10%, 20% and 30%).

Yield: 95%

Rf = 0.15 (2% $NH_3 \cdot H_2O$ and 20% ^iPrOH in $CHCl_3$)

LC/MS: $M+H^+ = 516$ (2CN column)

^1H NMR (200 MHz, CD_3OD): 7.29 (s, 1H), 7.62 (s, 1H), 7.42-7.40 (m, 2H), 7.05-6.85 (m, 2H), 5.5 (s, 2H), 4.20-4.02 (m, 2H), 3.25-3.10 (m, 1H), 2.92-2.72 (m, 2H), 1.45 (s, 9H), 1.28 (s, 3H).

(2) N-Boc compound (0.02 mmol) was placed in a 2-drum vial with a stirbar, and

hydrochloric acid in dioxane (6.0 M, 500 L) was added. The mixture was stirred at room temperature for 30 minutes to give the corresponding product as precipitate (hydrochloride salt). The mixture was centrifuged, the solution removed using a pipette, and the solid salt was dried under vacuum over night.

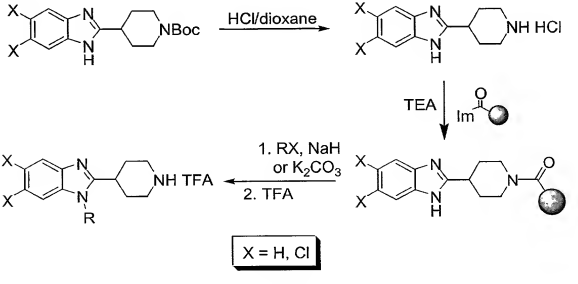
Yield: 90%

LC/MS: $M+H^+ = 202$ (2G column)

Example 4

General Procedure for Preparation of Benzimidazole Derivatives via Solid Phase Synthesis

The general procedure for preparation of benzimidazole derivatives via solid phase synthesis is shown in Scheme 4, below:



Scheme 4

(1) N-Boc-4,5-dichlorobenzimidazole (3.0 mg, 10.7 mmol) was powdered and treated with hydrogen chloride in dioxane (6 N) for 2 h. Dioxane was then evaporated and the corresponding hydrochloride salt was dried under vacuum overnight, which was directly used to attach to the Wang resin

(2) Wang resin (15.0 g, 5.70 mmol) (Sigma-Aldrich 2000-2001 Catalog, item # 47,703-6) was swollen in DMF (120 mL), and carbonyl diimidazole (1.84 g, 11.4 mmol) was added and the resulting mixture stirred at room temperature overnight. The resin was

filtered off and washed successively with DMF (3X30 mL), dichloromethane (3X30 mL), diethyl ether (3X30 mL) and dried overnight. The resulting resin was again suspended in DMF (200 mL), all the benzimidazole hydrochloride salt obtained in step (1) was added, followed by triethylamine (3.0 mL, 21.6 mmol). The resulting mixture was stirred at room temperature overnight. The resin was filtered off and washed successively with DMF (3X30 mL), dichloromethane (3X30 mL), methanol (3X30 mL), diethyl ether (3X30 mL) and dried overnight.

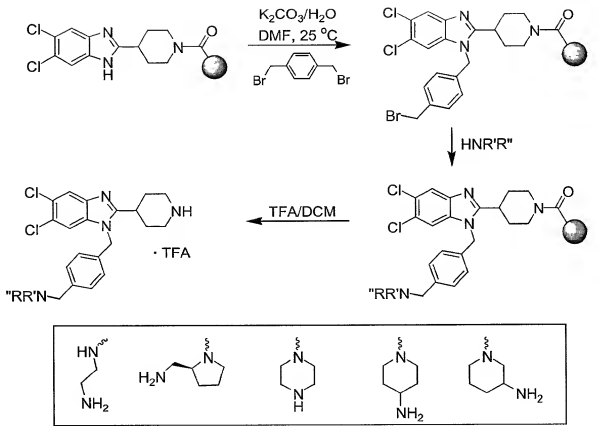
(3) Benzimidazole on Wang resin obtained in step (2) (100 mg, ~0.0324 mmol) was suspended in DMF (2.0 mL), sodium hydride (60%, 50 mg, 1.25 mmol) was added and the mixture stirred for 15 minutes at room temperature. Alkylating halide (0.0972 mmol) was added, and the mixture was stirred for 2 hours at room temperature. The reaction flask was then cooled with ice bath, and water (100 L) was carefully added to react with the excess sodium hydride. The resin was filtered off and washed successively with water ((3X1.0 mL), DMF (3X1.0 mL), dichloromethane (3X3=1.0 mL), methanol (3X1.0 mL), diethyl ether (3X1.0 mL) and dried overnight.

(4) The resin obtained in step (3) was suspended in dichloromethane (1.4 mL), trifluoroacetic acid (600 L) was added and the mixture was gently stirred for 30 minutes at room temperature. The resin was then filtered off and washed with dichloromethane (5 X 1.0 mL). The dichloromethane solution was dried to give the benzimidazoles as trifluoroacetic acid salt.

Example 5

General Procedure for Preparation of Xylene-1-yl Benzimidazole Derivatives via Solid Phase Synthesis

The general procedure for preparation of xylene-1-yl benzimidazole derivatives via solid phase synthesis is shown in Scheme 5, below:



Scheme 5

(1) Benzimidazole on Wang resin (2.0 g, ~0.65 mmol) was suspended in DMF (20.0 mL), saturated potassium carbonate (2.0 mL) was added, followed by *a,a'*-dibromo-*p*-xylene (860 mg, 3.25 mmol), and the resulting mixture was gently stirred at room temperature for 5 hours. The resin was filtered off and washed successively with water ((3X.0 mL), DMF (3X10.0 mL), dichloromethane (3X3=10.0 mL), methanol (3X10.0 mL), diethyl ether (3X10.0 mL) and dried overnight.

(2) Benzyl bromide on resin obtained instep (1) (100 mg, 0.0324 mmol) was suspended in DMF (2.0 mL), and amine (0.324 mmol) was added. The reaction mixture was gently stirred at room for six hours. The resin was filtered off and washed successively with DMF (3X1.0 mL), dichloromethane (3X3=1.0 mL), methanol (3X1.0 mL), diethyl ether (3X1.0 mL) and dried overnight.

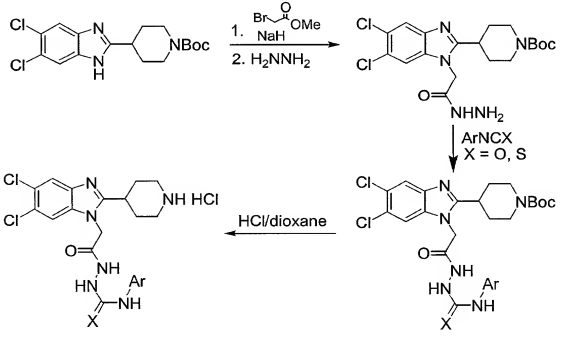
(3) The resin obtained in step (1) was suspended in dichloromethane (1.4 mL), trifluoroacetic acid (600 L) was added and the mixture was gently stirred for 30 minutes

at room temperature. The resin was then filtered off and washed with dichloromethane (5X1.0 mL). The dichloromethane solution was dried to give the benzimidazoles as trifluoroacetic acid salt.

Example 6

General Procedure for Preparation of Benzimidazole Derivatives Having Urea or Thiourea Functionality

The general procedure for preparation of benzimidazole derivatives having urea or thiourea functionality is shown below in Scheme 6:



Scheme 6

(1) To a solution of N-Boc benzimidazole (200 mg, 0.54 mmol) in DMF (2.0 mL) was added sodium hydride (60%, 65 mg, 1.40 mmol) portion-wise, and the resulting mixture was stirred for 20 minutes. Methyl bromoacetate (214 mg, 1.40 mmol) was then added and the reaction mixture was stirred at room temperature for 2 hours. The reaction flask was then cooled with ice bath, and water (100 μL) was carefully added to react with the excess sodium hydride. The resulting mixture was then diluted with ethyl acetate (30 mL), washed with brine (5X2 mL) and dried over magnesium sulfate. The crude product

was purified on silica gel with 50% ethyl acetate in hexane to give 210 mg (88%) of the desired methyl ester. (1815-41)

Rf = 0.40 (AcOEt : Hexane = 1:1)

LC/MS: $M+H^+ = 442$ (2CN column)

^1H NMR (200 MHz, $CDCl_3$): 7.80 (s, 1H), 7.38 (s, 1H), 4.95 (s, 2H), 4.40-4.15 (m, 3H), 3.78 (s, 3H), 3.00-2.78 (m, 2H), 2.10-1.80 (m, 6 H).

(2) To the solution of methyl ester (160 mg, 0.36 mmol) obtained form step 1) in methanol (5.0 mL) was added hydrazine (46.0 mg, 1.44 mmol), and the resulting mixture was stirred at room temperature for three hours. The reaction was then concentrated and the crude product purified on silica gel with 10% methanol in chloroform to give the corresponding acyl hydrazine (152 mg, 92%) Rf = 0.15 (MeOH : $CHCl_3$ = 1:1)

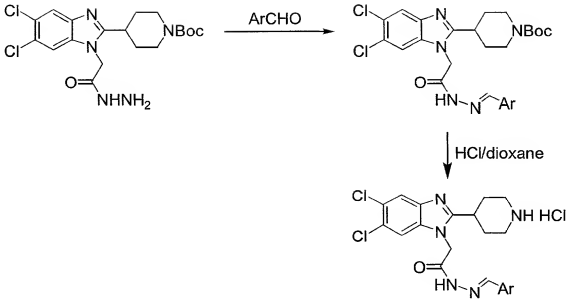
(3) To the solution of acyl hydrazine (30 mg, 0.068 mmol) obtained from step 2) in chloroform (2.0 mL) was added isocynate or isothiocynate (0.068 mmol) at 0C, and the reaction was warmed up and stirred at room temperature for one hour. TLC and LC/MS indicated complete conversion of the starting material and the product has more than 90% purity.

(4) Urea or thiourea (0.02 mmol) obtained in step 3) was powdered and treated with hydrogen chloride in dioxane (6 N) for 2 h. Dioxane was then evaporated and the corresponding hydrochloride salt was dried under vacuum overnight. LC/MS indicated complete conversion of starting material and desired product has over 90% purity.

Example 7

General Procedure for Preparation of Benzimidazole Derivatives Having Hydrazone Functionality

The general procedure for preparation of benzimidazole derivatives having hydrazone functionality si shown below in Scheme 7:



Scheme 7

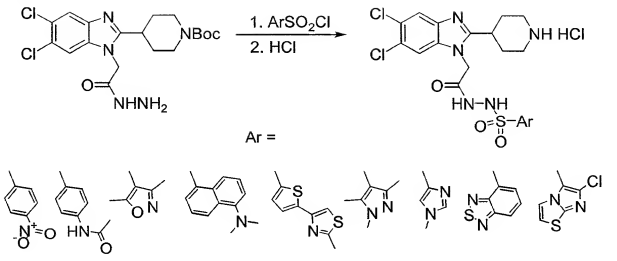
(1) To the solution of acyl hydrazine (20 mg, 0.045 mmol) and aldehyde (0.0475 mmol) in THF (1.0 mL) was added catalytic amount of p-tolunesulfonic acid. The reaction mixture was stirred at room temperature for two hours, and dried. TLC and LC/MS indicated complete conversion of starting material and desired product has over 90% purity.

(2) Half of the N-Boc hydrazone obtained above (0.023 mmol) was powdered and treated with hydrogen chloride in dioxane (6 N) for 30 min. Dioxane was then evaporated and the corresponding hydrochloride salt was dried under vacuum overnight. LC/MS indicated complete conversion of starting material and desired product has over 90% purity.

Example 8

General Procedure for Preparation of Benzimidazole Derivatives Having Sulfonamide Functionality

The general procedure for preparation of benzimidazole derivatives having sulfonamide functionality si shown below in Scheme 7:



Scheme 8

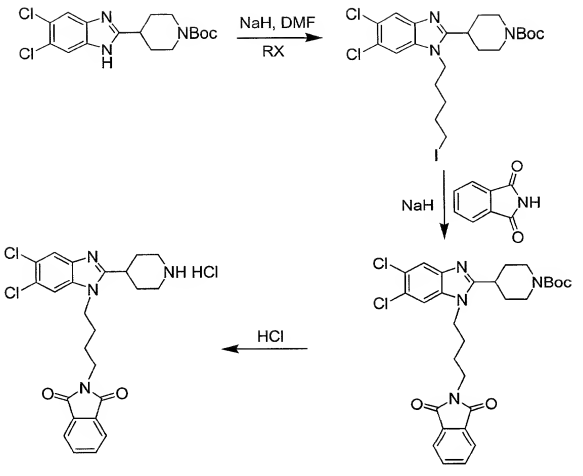
(1) To the solution of acyl hydrazine (20 mg, 0.045 mmol) and pyridine (6.0 mg, 0.072 mmol) and DMAP (catalytic) in 30% THF in CH_2Cl_2 was added sulfonyl chloride (0.0475 mmol). The reaction mixture was stirred at room temperature overnight, and dried. TLC and LC/MS indicated complete conversion of starting material and desired product has over 90% purity.

(2) Half of the N-Boc sulfonamide obtained above (0.023 mmol) was powdered and treated with hydrogen chloride in dioxane (6 N) for 2 h. Dioxane was then evaporated and the corresponding hydrochloride salt was dried under vacuum overnight. LC/MS indicated complete conversion of starting material and desired product has over 90% purity.

Example 9

General Procedure for Preparation of Benzimidazole Derivatives Having Substituted Alkyl Functionality

The general procedure for preparation of benzimidazole derivatives having substitutued alkyl functionality is shown below in Scheme 9. While the procedure is illustrated for phthalimidyl-alkyl functionalization, the procedure is generally applicable to to the preparation of benzimidazoles having a wide variety of heterocycles attached through alkyl spacers.



Scheme 9

(1) To the solution of N-Boc benzimidazole (110 mg, 0.30 mmol), and diiodide (1.50 mmol) in DMF (3.0 mL) was added sodium hydride (60%, 120 mg, 3.0 mmol) portion-wise. After the reaction mixture was stirred at room temperature for 20 minutes, the reaction flask was then cooled with ice bath, and water (100 mL) was carefully added to react with the excess sodium hydride. The resulting mixture was then extracted with ethyl acetate (3X10 mL) and the combined organic solution was Washed with brine and dried over magnesium sulfate. The crude product was purified on silica gel with 50% ethyl acetate in hexane.

Rf = 0.55 (AcOEt : Hexane = 1:1)

LC/MS: $M+H^+ = 567$ (2CN column)

^1H NMR (200 MHz, $CDCl_3$): 7.75 (s, 1H), 7.35 (s, 1H), 4.35-4.15 (m, 1H), 4.20-3.95 (m, 2H), 3.20-3.00 (m, 2H), 2.00-1.20 (m, 12 H).

(2) To the solution of iodo benzimidazole obtained in step 1) (0.044 mmol), phthalimide or amide (0.066 mmol) in DMF (1.5 mL) was added potassium carbonate (11

mg, 0.066 mmol). After being stirred at room temperature overnight, the reaction mixture was diluted with 50 mL of ethyl acetate, washed with brine (5X2 mL), dried over magnesium sulfate and concentrated. The crude product was purified on silica gel with 50% ethyl acetate in hexane.

Rf = 0.40 (AcOEt : Hexane = 1:1)

LC/MS: $M+H^+ = 631$ (2CN column)

^1H NMR (200 MHz, $CDCl_3$): 8.70-8.55 (m, 3H), 8.10-8.00 (m, 1H), 7.78 (s, 1H), 7.41 (s, 1H), 4.40-4:00 (m, 3H), 3.82 –3.70 (m, 2H), 3.08-2.80 (m, 2H), 2.00-1.20 (m, 12 H).

Example 10

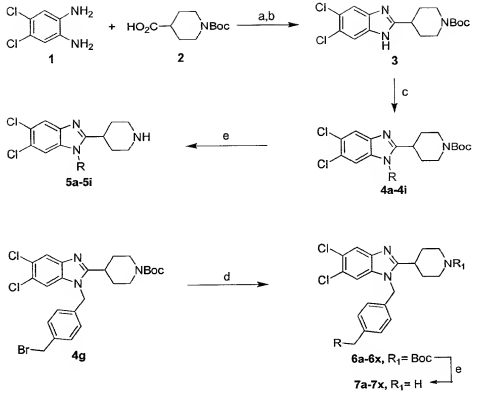
Biological Evaluation of Compounds

Compounds were evaluated for in vitro antibacterial activity (referred to MIC, the minimum concentration inhibiting fungal cell growth) against S. aureus and E. coli. Table 2 shows the in vitro inhibitorial activity of selected benzimidazoles against additional pathogenic strains of bacteria (four Gram positive strains, four gram negative strains and one yeast strain). The assays are carried out in 150 mL volume in duplicate in 96-well clear flat-bottom plates. The bacterial or yeast suspension from an overnight culture growth in appropriate medium is added to a solution of test compound in 2.5% DMSO in water. Final bacterial or yeast inoculum is approximately 10^2-10^3 CFU/well. The percentage growth of the bacteria or yeast in test wells relative to that observed for a control well containing no compound is determined by measuring absorbance at 595 nm (A_{595}) after 20-24 hours at 37°C (bacteria) or 40-48 hours (yeast) at 25°C. The MIC is determined as a range of concentration where complete inhibition of growth is observed at the higher concentration and bacterial/yeast cells are viable at the lower concentration. Ampicillin and tetracycline are used as antibiotic positive controls for bacterial MIC assays. Amphotericin B is used as a positive control for yeast MIC assay.

Example 11

Preparation of 5,6-dichloro-2-piperidin-4-yl Benzimidazole Derivatives

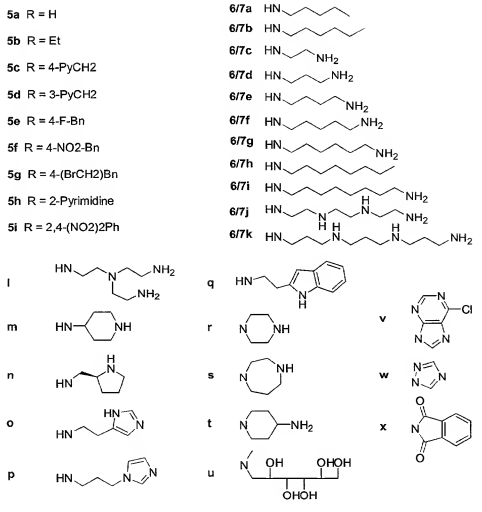
Using the procedures described above, the following 5,6-dichloro-2-piperidin-4-yl benzimidazole derivatives prepared according to Scheme 11 as described below:



Scheme 11

Treatment of commercially available 4,5-dichloro-1,2-phenylenediamine **(VENDOR?) (1)** and N-Boc-isonipecotic acid **(2)** with EDC in the presence of catalytic amount of DMAP led to the formation of the corresponding amide. The crude mixture was then refluxed in aqueous sodium hydroxide solution to give cyclized intermediate **3**, which was reacted with various alkyl, benzyl and aryl halides to give **4a-4l**. Treatment of compound **4g** with various amines or nitrogen-containing heterocylces provided **6a-x.** Deprotection of the Boc group with anhydrous hydrogen chloride (HCl, 4.0 M) in dioxane at room temperature for 30 minutes to form benzimidazoles **7a-x**. In a similar manner, **4a-4l** were treated with hydrogen chloride to give benzimidazoles **5a-i**.

This procedure was employed to prepare the following compounds:



These compounds were evaluated for their ability to inhibit S. aureus and E. coli growth and Bacterial Transcription/Translation according to the procedures described herein. In addition, all benzimidazoles were also screened for their ability to inhibit bacterial translation and transcription using a combined assay. Several compounds (**7c, 7d, 7j-l, 10a-b**) were found to posses low micromolar IC50. Since most of the IC50 value are much higher than the corresponding MICs for S. aeures and E. coli., it's unlikely that the antibacterial activities are the direct results of bacterial transcription/translation inhibition. However they could be a result from the combination of multiple mechanisms of actions including transcription/translation inhibition. The results are presented in Table 1 below:

Table 1

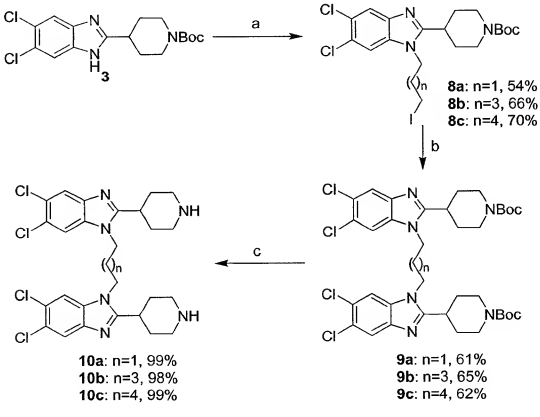
Inhibitory Effects of Benzimidazoles on S. aureus and E. coli Growth and Bacterial Transcription/Translation.

Compounds	S.aureus MIC (μM)	E.coli MIC(μM)	T/T IC50 MIC (μM)
(5a)	>100	>100	>100
(5b)	>100	>100	>100
(5c)	75.00	94	>100
(5d)	75.00	86	>100
(5e)	>100	>100	>100
(5f)	>100	>100	>100
(4g)	52.00	>100	>100
(5h)	>100	>100	>100
(5i)	>100	>100	>100
(7a)	6-12	12-25	100
(7b)	3-6	6-12	>100
(7c)	6-12	12-25	12
(7d)	12-25	50-100	20
(7e)	6-12	25-50	50
(7f)	12-25	25-50	>100
(7g)	6-12	12-25	100
(7h)	12-25	50-100	>100
(7i)	6-12	6-12	>100
(7j)	6-12	50-100	10
(7k)	3-6	25-50	10
(7l)	3-6	12-25	10
(7m)	6-12	12-25	>100
(7n)	12-25	12-25	>100
(7o)	6-12	12-25	25
(7p)	12-25	12-25	>100
(7q)	--	--	--
(7r)	6-12	12-25	>100
(7s)	6-12	12-25	>100
(7t)	6-12	50-100	60
(7u)	6-12	25-50	>100
(7v)	>100	>100	12-25
(7w)	12-25	12-25	>100
(7x)	6-12	6-12	>100
(10a)	25-50	25-50	25
(10b)	12-25	12-25	35
(10c)	6-12	12-25	>100
(12)	3-6	6-12	>100

Example 12

Preparation of Benzimidazole Dimers

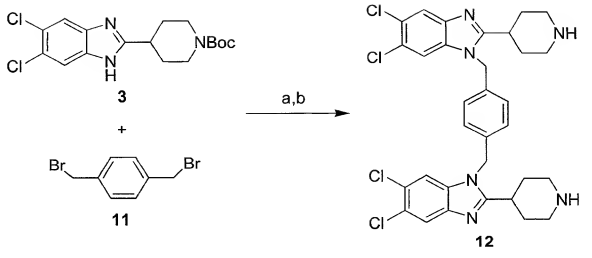
Several benzimidazole dimers were prepared according to the procedures of Schemes 12 and 13, below, and evaluated for their antibacterial activity.



Scheme 12

Synthesis of Benzimidazole Dimers 10a-c

Reagents and conditions: a) NaH, DMF, 0°C, 2 h, 1,3-diiodopropane, **8a,** 54%; 1,5-diodopentane, **8b**, 66%; 1,6-diodohexane, **8c**, 70%; (b) **3**, NaH, DMF, 0°C, 2 h, 61% for **9a**, 65% for **9b**, 62% for **9c**; (c) 6 MHCl/dioxane, 25°C, 2h.



Scheme 13
Synthesis of Benzimidazole Dimer **12**

Reagents and conditions: a) 0.5 equiv. α,α-dibromo-*p*-xylene, NaH, DMF, 0°C, 2 h, 56%; (b) 4 M HCl/dioxane, RT, 2h, 98%.

Mono alkylation of benzimidazole with diiodo alkanes provided intermediates **8a-c**, which were then reacted again with **3** to provide the corresponding dimers **9a-c**. The Boc protecting groups were cleanly removed using hydrogen chloride in dioxane to give the final dimer analogs **10a**, **10b** and **10c** in almost quantitative yield (Scheme 12). The xylene-spaced dimer **12** was prepared from intermediate **3** by first reacting 0.5 equivalents of α,α-dibromo-p-xylene (**11**), followed by deprotection using hydrogen chloride (Scheme 13).

The inhibitory effects of benzimidazole dimers on S. aureus and E. coli growth and bacterial transcription/translation are shown in Table 2 below.

Table 2

Inhibitory Effects of Benzimidazole Dimers on S. aureus and E. coli Growth and Bacterial Transcription/Translation.

Compounds	S.aureus MIC (μM)	E.coli MIC(μM)	T/T IC50 MIC (μM)
(10a)	25-50	25-50	25
(10b)	12-25	12-25	35

(10c)	6-12	12-25	>100
(12)	3-6	6-12	>100

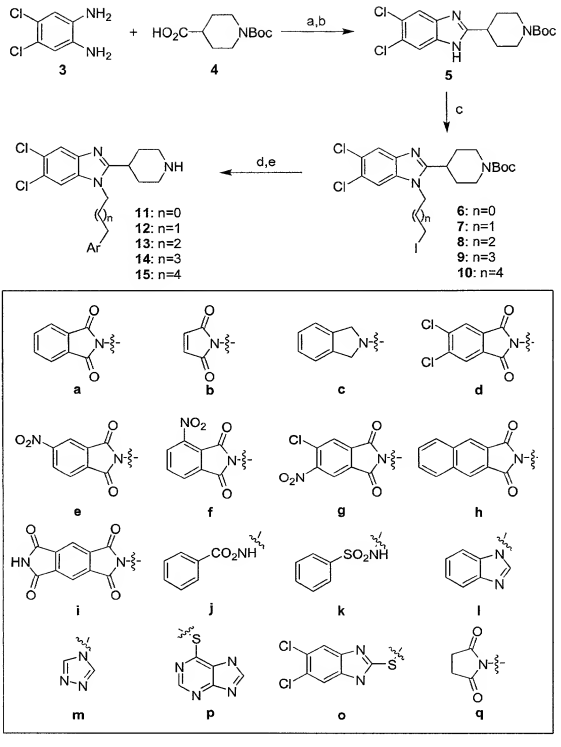
To test effectiveness of benzimidazoles of Examples 11 and 12 against other bacteria, the active compounds from the preliminary screening were screened against additional four strains of Gram positive and four strains of gram negative bacteria, and the results are shown in Figure 1. These compounds exhibited higher potencies against Gram position bacteria (S. aureus 13709, E. hirae 29121, S pyogenes 49399, and S. pneumoniae 6303) as compared to Gram-negative bacteria (E. coli 25922, P. vulgaris 8427, K. pneumoniae 1338, P. aeruginosa 25416). Several benzimidazoles (7b, 7g-k, 12) showed particularly strong activity against E. hirae. To study the selectivity, these compounds were also screened against yeast cell line C. albicans 10231. These compounds are clearly much less effective as compared to their inhibition of bacterial growth.

Since entercocccus infection is upcoming, and presents a major threat to the human health, compounds were screened against seven additional clinically important strains of entercocccus and the results are shown in Figure 2. As mentioned previously, all these selected compounds are very effective against E. Hirae_ATCC_29212 and less potent against other strains with some exceptions that six of them **(7a, 7b, 7x, 10b, 10c, 12)** exhibited strong inhibitory activities against all eight strains.

Example 13

Preparation of Alkyl Spaced Benzimidazole Derivatives

Several alkyl spaced benzimidazole derivatives were prepared according to the procedures of Scheme 14, below:


3
4
a,b
5
c
6: n=0
7: n=1
8: n=2
9: n=3
10: n=4
d,e
11: n=0
12: n=1
13: n=2
14: n=3
15: n=4
a
b
c
d
e
f
g
h
i
j
k
l
m
p
o
q

Scheme 14

Alkyl Spaced Benzimidazole Derivatives

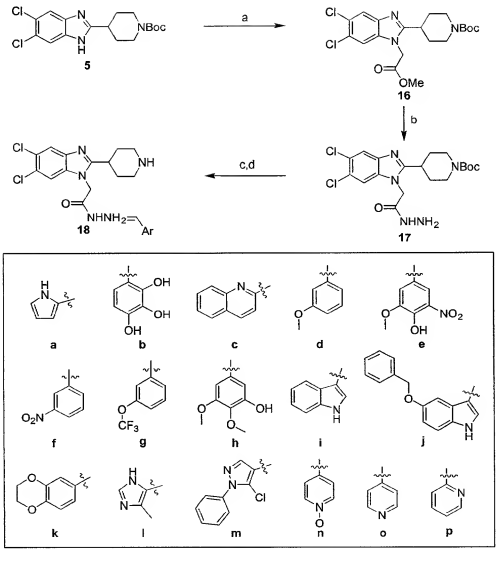
Reagents and conditions: a) EDC, DMAP; b) . NaOH, H_2O, 65% over 2 steps; c) $ICH_n(CH_n)_nCH_nI$, NaH or K_2CO_3; d) ArH, NaH or K_2CO_3; e) 4.0 M HCl/dioxane, CH_2Cl_2, 25 °C, 0.5 h, >95%.

4,5-dichloro-1,2-dianiline (**1**) reacted smoothly with N-Boc-isonipecotic acid to give the corresponding amide, which cyclized upon treatment with sodium hydroxide to give benzimidazole **5**. Reaction of **5** with different diiodides furnished **6-10** in good yields. A variety of nitrogen-containing heterocylces were then introduced by simple alkylation to give the target molecules **11-15**.

Example 14

Preparation of Hydrazone Benzimidazole Derivatives

Several hydrazone benzimidazole derivatives were prepared according to the procedures of Scheme 15 below:



Scheme 15

Preparation of Hydrazone Benzimidazole Derivatives

Reagents and conditions: a). NaH (3.0 equiv), $BrCH_2CO_2Me$ (1.2 equiv), DMF, 25 °C, 0.5 h, 92%; B). H_2NNH_2 (5.0 equiv), DMF, 25 °C, 2.0 h, 98%; c). ArCHO (1.02 equiv), CH_2Cl_2, 25 °C, 0.5 h, >95%; d). 4.0 M HCl/dioxane, CH_2Cl_2, 25 °C, 0.5 h, >95%.

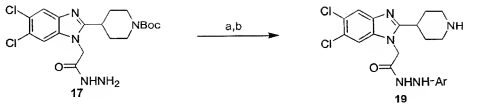
Acylhydrazide **17** was synthesized as a key intermediate for the combinatorial generation of benzimidazoles. Since the acyl hydrazide could serve as both a hydrogen donor and acceptor to add additional contacts with the target, analogs based on **17** could be potentially more potent than the parent benzimidazoles. Acycl hydrazide **17** was easily prepared from **3** in gram quantity in excellent overall yield from **5** by alklylation with methyl α-bromoacetate followed by a nucleophilic displacement of the methoxy group. Many derivatives could be easily synthesized form **17** without the need of vigorous

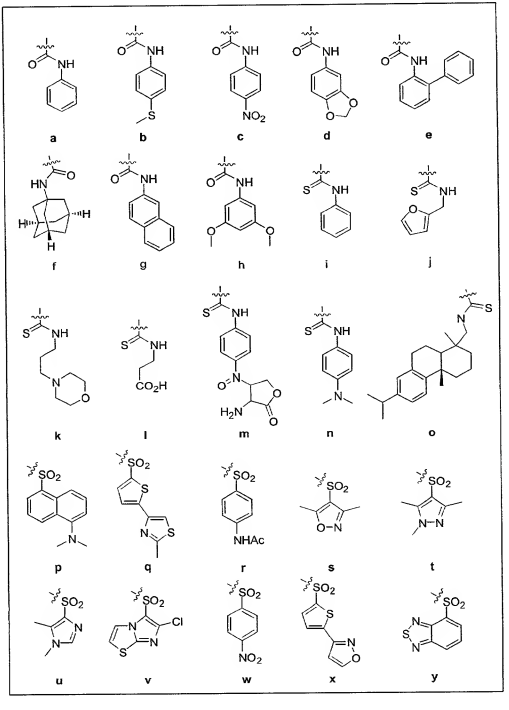
purification. The first series of analogs has the general structure **18** and was prepared by simply reacting **17** with different aldehydes followed by the removal of the Boc protecting group with hydrogen chloride. All the benzimidazole analogs obtained this way have more than 95% purity based on TLC and LC/MS analysis and were used directly for our MS-based screening and antibacterial assays.

Example 15

Preparation of Hydrazine Benzimidazole Derivatives

Several hydrazine benzimidazole derivatives were prepared according to the procedures of Scheme 16 below:





Scheme 16

Hydrazine Benzimidazole Derivatives

Synthesis of Benzimidazoles 19a-19y. Reagents and conditions: a) For 19a-o, RNCO or RNCS (1.05 equiv), CH_2CH_2, 25 °C, 0.5 h, >95%.; for 19p-y, RSO_2Cl (1.05 equiv), Et_3N (1.5 equiv), DMAP (cat.), >95%; b) 4.0 M HCl/dioxane, CH_2Cl_2, 25 °C, 0.5 h, >95%.

A variety of isocyanates, isothiocyanates and sulfonyl chlorides were reacted with acyl hydrazide **17**, and the corresponding ureas, thioureas and sulfonates were obtained in excellent yields and purity as shown in Scheme 16. The resulting N-Boc protected intermediates were treated with hydrogen chloride to give the corresponding products of general structure **19** in almost quantitative yields and more than 95% purity. These products were used directly for antibacterial assays.

Example 16

Inhibitory Effects of Benzimidazoles on S. aureus and E. coli Growth and Bacterial Transcription/Translation For Compounds of Examples 13-15.

Table 3 shows the in vitro antibacterial activity (referred to as MIC, the minimum concentration inhibiting fungal cell growth) of the benzimidazoles against S. aureus and E. coli. Figure 3 shows the in vitro inhibitorial activity of selected benzimidazoles against additional pathogenic strains of bacteria (four Gram positive strains, four gram negative strains and one yeast strain). The assays are carried out in 150 μL volume in duplicate in 96-well clear flat-bottom plates. The bacterial or yeast suspension from an overnight culture growth in appropriate medium is added to a solution of test compound in 2.5% DMSO in water. Final bacterial or yeast inoculum is approximately 10^2-10^3 CFU/well. The percentage growth of the bacteria or yeast in test wells relative to that observed for a control well containing no compound is determined by measuring absorbance at 595 nm (A_{595}) after 20-24 hours at 37°C (bacteria) or 40-48 hours (yeast) at 25°C. The MIC is determined as a range of concentration where complete inhibition of growth is observed at the higher concentration and bacterial/yeast cells are viable at the lower concentration. Ampicillin and tetracycline are used as antibiotic positive controls for bacterial MIC assays. Amphotericin B is used as a positive control for yeast MIC assay.

Table 3

Inhibitory Effects of Benzimidazoles on S. aureus and E. coli Growth and Bacterial Transcription/Translation.

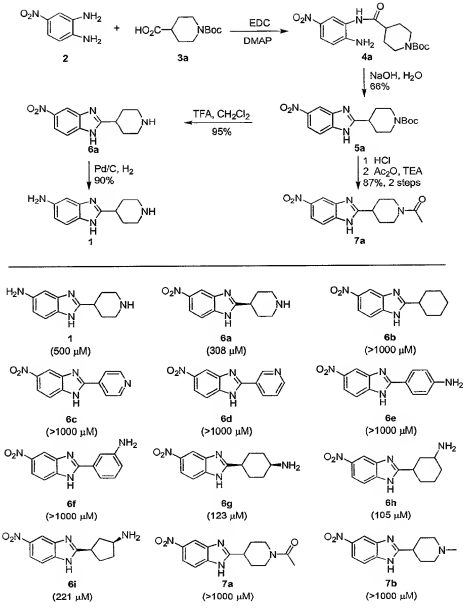
Compound	S. aureus MIC (mM)	E. coli MIC (mM)
6	>100	>100
11	>100	>100
12	>100	>100
13a	>100	>100
13o	>100	>100
13p	>100	>100
14a	12-50	25-50
14b	6-12	>100
14c	50-100	25-50
14d	12-25	50-100
14e	>100	50-100
14f	>100	>100
14g	25-50	50-100
14h	>100	>100
14i	>100	>100
14j	>100	>100
14k	>100	>100
14l	>100	>100
14l	50-100	50-100
14q	>100	>100
15a	>100	>100
18a	12-25	>100
18b	12-25	>100
18c	25-50	>100
18d	25-50	>100
18e	25-50	>100
18f	25-50	>100
18h	25-50	>100
18i	25-50	>100
18j	3-6	>100
18k	50-100	>100
18l	50-100	>100
18m	6-12	>100
18n	>100	>100
18o	>100	>100
18p	>100	>100
18q	25-50	>100
19b	12-25	25-50
19c	25-50	>100

19c	12-25	25-50
19d	25-50	50-100
19e	50-100	>100
19f	6-12	12-25
19g	6-12	12-25
19h	6-12	25-50
19h	50-100	>100
19i	25-50	50-100
19j	50-100	>100
19k	>100	>100
19l	>100	>100
19m	>100	>100
19o	25-50	25-50
19p	12-25	>100
19q	50-100	>100
19r	>100	>100
19s	>100	>100
19t	>100	>100
19u	>100	>100
19v	>100	>100
19w	>100	>100
19x	>100	>100
19y	>100	>100

Example 17

Synthesis of Piperidine Modified Benzimidazoles and their Binding Affinities For E. coli 16S A-site

It has been established that the 16S A-site is involved in bacterial translation, and the aminoglycosides are known to bind to the region. Thus, the bacterial 16S A-site represents a prime target for discovering antibacterial agents, and much work has focused on the modification of the natural aminoglycosides. In accordance with the present invention, several small molecules were synthesized that were shown to bind to the 16S A-site of E. coli ribosome RNA. These are shown below in Scheme 17.



Scheme 17

Synthesis of piperidine-modified benzimidazoles and their binding affinities for E. coli 16S A-site

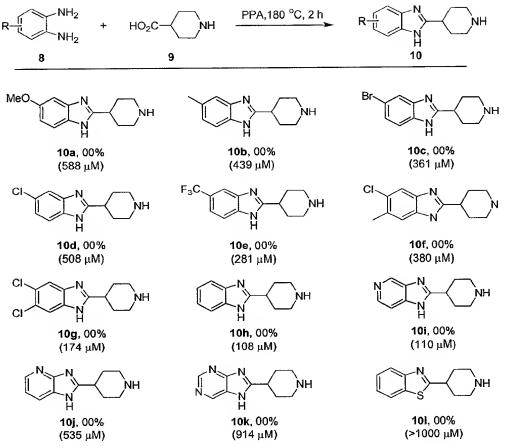
MS-based competition experiments were used to determine the binding location of **1** to the target RNA. Glucosamine is the A-ring of paromomycin that is known to bind to the target RNA and inhibits bacterial translation. Data suggest that **1** and glucosamine compete for the same binding site on the target RNA. Since glucosamine binds to the target RNA at the same location as it is in paromomycin binding, while not wishing to be bound by any particular theory, it is believed the **1** binds to the desired RNA decoding region and could potentially inhibit bacterial translations.

After establishing the binding of **1** to the correct location on the target RNA, systematic chemical modifications were carried out to study the structure activity relationship (SAR) around the benzimidazole. The synthesis of compound **1** and piperidine-modified benzimidazoles are shown above in Scheme 17. Treatment of commercially available 5-nitro-1,2-dianiline (**2**) and N-Boc-isonipecotic acid (**3**) with EDC in the presence of catalytic amount of DMAP led to the formation of the corresponding amide as a mixture of two regioisomers (**4a**,**b**). The crude mixture was then refluxed in aqueous sodium hydroxide solution for **??** hours gave the cyclized intermediate **6a**. Treatment of compound **5** with 20% TFA in dichloromethane at room temperature for 30 minutes led to the formation of compound **6**, which was then hydrogenated over Pd/C to give **1**. MS-based assay suggested that an electron withdrawing nitro group at C5 position (**6**) is preferred over the corresponding amino group (**1**), and almost doubled the binding affinity for the target 16S RNA A-site. Thus, in order to establish the SAR of the benzimidazoles, a series of piperidine-modified analogs with a nitro substitution at 5 position (**6a**-**7b**) were synthesized by following the same synthetic route and all these compounds were screened against 16S RNA A-site. A basic NH group with the correct orientation in this region is required to maintain the affinity, since acetylation (**7a**), methylation (**7b**), removal (**6b**) of the free NH group and unsaturation of the piperidine ring (**6c**) all diminished the binding affinity. The NH group is critical, presumably because it forms a hydrogen bond with the negatively charged phosphate in the RNA backbone. The extended piperidine analogs (**6g**-**6t**) showed improved affinities, which, while not wishing to be bound by any particular theory, are believed to better orient the NH groups to contact the phosphate backbone.

Example 18

One-Pot Synthesis of Benzimidazoles and Their Binding Affinities for E. coli 16S A-site

A series of piperidine substituted benzimidazoles were prepared according to the one-pot procedure of Scheme 18:



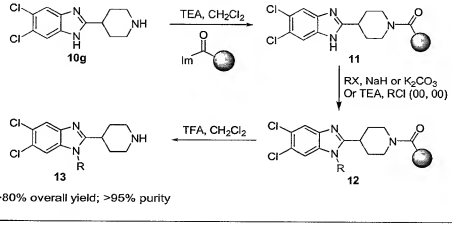
Scheme 18

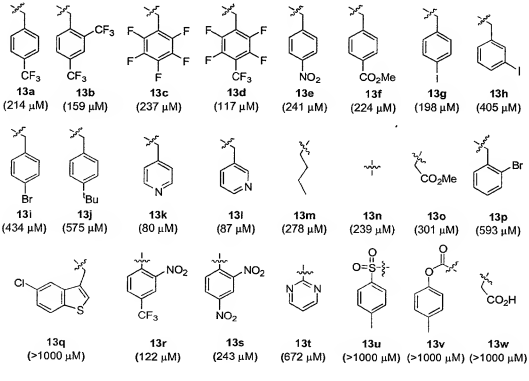
A series of benzimidazole-modified analogs were prepared as shown above. The procedure required the simple heating of a suitable 1,2-dianiline (**8**) with isonipecotic acid (**9**) in the presence of polyphosphoric acid. The free benzimidazoles were then isolated in good to excellent yields after basic work-up. From a MS-based assay, it was established that 1) An electron donating groups such as, NH_2 and OMe reduced the affinities (**1**, **10a**); 2) Certain hydrophobic substitutions such as a methyl (**10b**), bromo (**10c**) and chloro (**10d**) are tolerated; 3) Insertion of nitrogen atoms into the aromatic moiety (**10i-10k**), particularly at the C4 position (**10j**) reduced activities; and 4) Electron-withdrawing groups enhanced the affinities (10e-10g).

Example 19

Synthesis of Additional N-1 Substituted Benzimidazoles and Their Binding Affinities for E. coli 16S A-site

A further series of N-1 benzimidazole analogs were prepared according to Scheme 19 below:





Scheme 19

Solid-phase synthesis of N1 substituted benzimidazoles and their binding affinities for E. coli 16S A-site

This series of compounds were efficiently synthesized by employing the solid-phase chemistry shown in Scheme 19. Wang resin was first converted into imidazole carbonyl derivative, which was then allowed to react with compound **10g** to give common intermediate **32**. Compound **11** reacted readily with a variety of alkylating or acylating reagents to give the corresponding alkyl or acyl products, which after removal of Boc

group with 50% TFA in dichloromethane led to the desired N-1 substituted analogs in excellent yields and purity.

Example 20

Synthesis of Additional Benzimidazole Dimers and MIC and their Transcription/Translation activity

This series of assays is known to those of skill in the art, and other assays may be substituted therefore without deviating from the spirit and scope hereof.

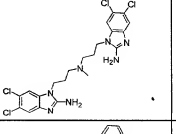
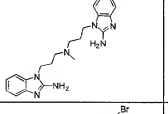
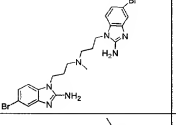
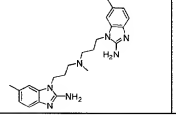
The DNA template, pBestLuc™ (Promega), is a plasmid containing a reporter gene for firefly luciferase fused to a strong *tac* promoter and ribosome binding site. Messenger RNA from 1 μg pBestLuc is transcribed and translated in *E. coli* S30 bacterial extract in the presence or absence of test compound. Compounds are tested in a black 96 well microtiter plate with an assay volume of 35 μL. Each test well contains: 5 μL test compound, 13 μL S30 premix (Promega), 4 μL 10X complete amino acid mix (1 mM each), 5 μL *E. coli* S30 extract and 8 μL of 0.125 μg/μL pBestLuc™. The transcription / translation reaction is incubated for 35 minutes at 37°C followed by detection of functional luciferase with the addition of 30 μL LucLite™ (Packard). Light output is quantitated on a Packard TopCount.

The assays are carried out in 150 μL volume in duplicate in 96-well clear flat-bottom plates. The bacterial suspension from an overnight culture growth in appropriate medium is added to a solution of test compound in 4% DMSO in water. Final bacterial inoculum is approximately 10^5-10^6 CFU/well. The percent growth of the bacteria in test wells relative to that observed for a well containing no compound is determined by measuring absorbance at 595 nm (A_{595}) after 24 h. The MIC is determined as a range of single compound where the complete inhibition of growth is observed at the higher concentration and cells are viable at the lower concentrations. Both ampicillin and tetracycline are used as antibiotic-positive controls in each screening assay for *S. pyogenes*, *E. coli*, *S. aureus*, *E. faecalis*, *K. pneumoniae* and *P. vulgaris*. Ciprofloxacin is used as an antibiotic positive control in each screening assay for *P. aeruginosa*.

Biological activity of selected compounds according to the present invention were assayed according to techniques known in the art.

A series of 2-aminobenzimidazole dimers were synthesized according to the procedure described in Example 11. A series of 5- and 6-substituted-2-aminobenzimidazoles also were synthesized, and all were evaluated for biological activity. Tables 4-7 report MIC and transcription/translation activity for the dimer compounds By the outlined procedure. Tables 8 and 9 report the MASS screening of 2-aminobenzimidazoles against the AgIIa HCV-IRES target. The reported selectivity was determined by mass spectral analysis of any associations and provides information about the relative binding affinities.

Table 4

Structure	MIC, *E. coli* (μM)	MIC, *S. aureus* (μM)	Transcription/ Translation, IC_{50} (μM)
	12-25	12-25	>100
	25-50	75-100	25
	25-50	25-50	>100
	>100	>100	6-12

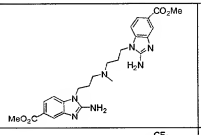
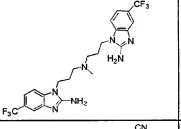
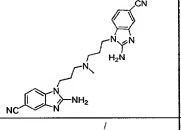
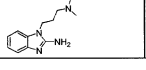
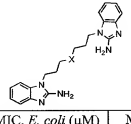
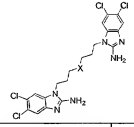
	>200	>200	>100
	25-50	50-100	>100
	>200	>200	>200
	>50	>50	>100

Table 5



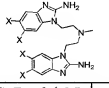
Structure	MIC, *E. coli* (μM)	MIC, *S. aureus* (μM)	Transcription/ Translation, IC_{50} (μM)
X=N(CH_3)$_2$	50-75	25-50	20
X=CH_2	>100	>100	>100
X=O	>100	>100	>100

Table 6



Structure	MIC, *E. coli* (μM)	MIC, *S. aureus* (μM)	Transcription/ Translation, IC_{50} (μM)
X=N-Me	25-50	75-100	25
X=CH_2	>100	>100	>100
X=O	6-12	>100	>100

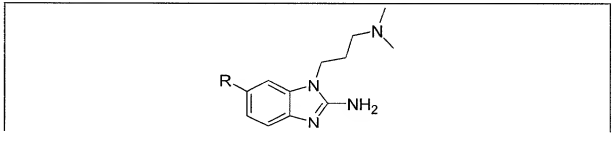
Table 7



Structure	MIC, *E. coli* (μM)	MIC, *S. aureus* (μM)	Transcription/ Translation, IC_{50} (μM)
X=H	>100	>100	>100
X=Cl	>100	>100	>100

Table 8

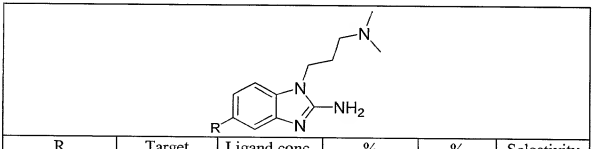
MASS Screening of 6-Substituted-2-aminobenzimidazoles against Ag IIa HCV IRES Target



R	Target conc. (μM)	Ligand conc. (μM)	% Complex	% Dimer	Selectivity
H	2.5	50	125	35	4.30
H	2.5	7.5	33	3	7.49
CH_3	2.5	50	136	31	6.55
CH_3	2.5	7.5	26	0	8.44
OCH_3	2.5	50	286	39	10.67
OCH_3	2.5	7.5	52	4	12.89
$O(CH_2)_3N(CH_3)_2$	2.5	50	862	72	96.88
$O(CH_2)_3N(CH_3)_2$	2.5	7.5	46	0	34.53

Table 9

MASS screening of 5-substituted-2-aminobenzimidazoles against Ag IIa HCV IRES Target



R	Target conc. (μM)	Ligand conc. (μM)	% Complex	% Dimer	Selectivity
H	2.5	50	125	35	4.30
H	2.5	7.5	33	3	7.49
CH_2NH_2	2.5	7.5	14.7	0	2.0
CH_2NH_2	2.5	50	109	80	2.3

It is intended that each of the patents, applications, and printed publications including books mentioned in this patent document be hereby incorporated by reference in their entirety.

As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.